Moving Forward in the Neuropsychological Assessment and Neuropsychiatric Care of Individuals with OMAS

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Hannah-Lise Schofield, PhD

April 12, 2025

Plan for today

- Introduction: Lim Ming
- Neuropsychiatry of OMAS: Aaron Hauptman
- Neuropsychology of OMAS: Hannah Schofield
- Models and Comparisons: Aaron Hauptman
- Recap and summary (what problem are we solving): Hannah Schofield
- Discussion of guidelines and next steps: Aaron Hauptman and Hannah Schofield
- Open discussion among attendees

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Neuropsychiatry of OMAS

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JOHNS HOPKINS
MEDICINE

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Disclosures

- Royalties from Springer Publishing for the text *Pediatric Neuropsychiatry: A Case-Based Approach*
- Honoraria from academic institutions for CME teaching activities on subject of pediatric neuropsychiatry

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Defining the fields

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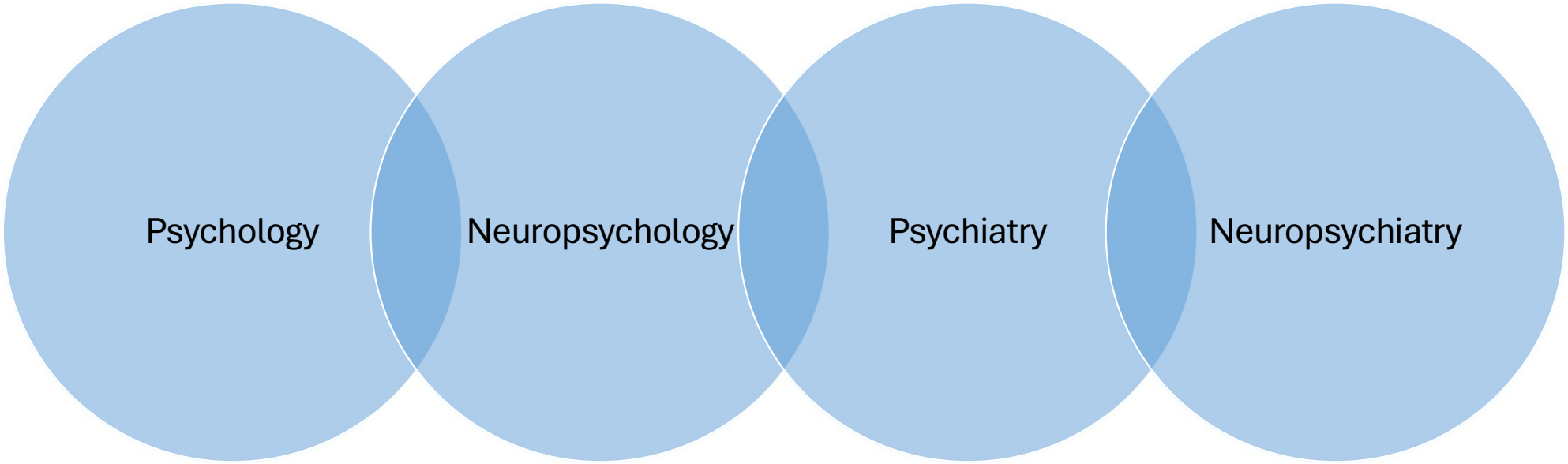

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Neuropsychology

- PhD/PsyD
- Neuropsychological testing
- Evaluation of cognitive domains
- Contextualization of development, behavior, emotional states
- Recommendations based on testing results, other findings and behavioral observations

<u>Evaluation</u>
Emotion
Behavior
Cognition
Psychological

<u>Integration</u>:
Developmental/
Medical data

<u>Recs:</u>
Behavioral/
Therapeutic
interventions

Neuropsychiatry

- MD/DO/MBBS
- Clinical assessment
- Integrated evaluation of neurological and psychiatric symptoms
- Focus on DSM-5 categories
- Assessment leads to psychotherapeutic and other recommendations, pharmacotherapeutic treatment

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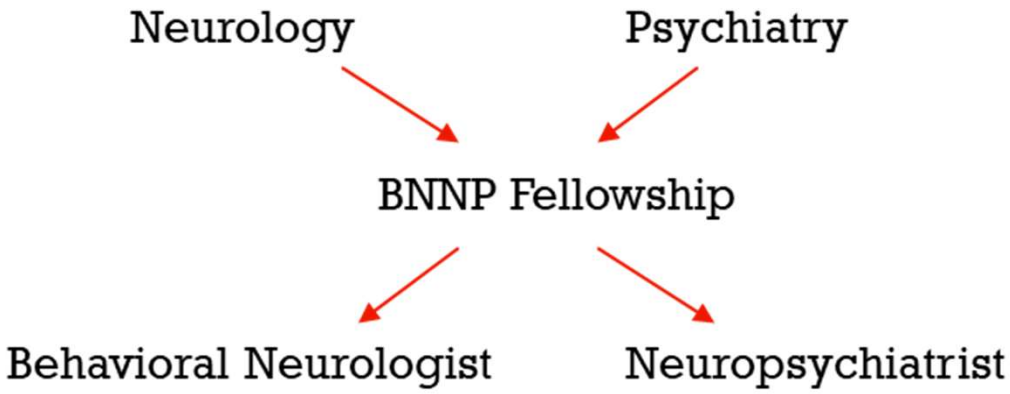
Neuropsychiatry

"The neuropsychiatrist is…ideally suited to evaluate and treat patients who have abnormalities in perception, cognition, emotion, and/or behavior due to a known psychiatric or neurologic disorder; due to the simultaneous presence of, or interaction between, psychiatric and neurologic disorders (or their treatments), and associated psychosocial elements; or due to an unknown underlying brain condition."

David Silbersweig, MD

from Neuropsychiatry and Behavioral Neurology: Principles and Practice



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Neuropsychiatric features of OMAS

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Behavioral trials

- Papero et al 1995
  - 13 children age 20 months to 16 years evaluated up to 12 years after onset
  - Behavior assessed with the Achenbach Child Behavior Checklist and Vineland, clinical observation
  - Borderline or above elevations for 7/8 subjects not on medication
  - 4 had history of aggression, but none showed significant elevation of externalizing on CBCL

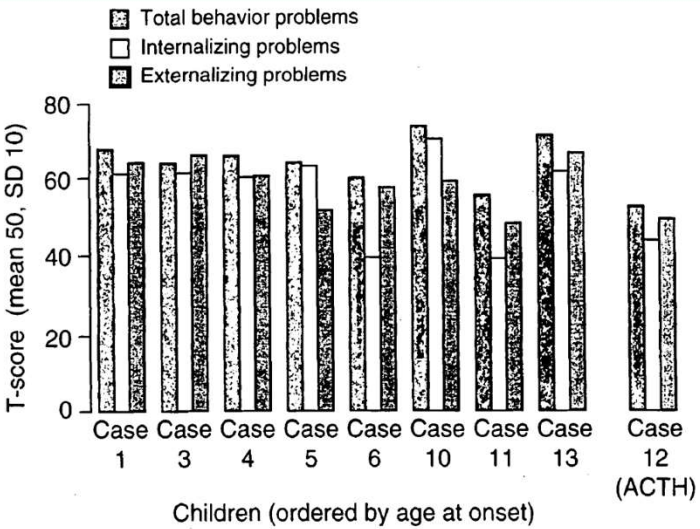


Fig. 2. Achenbach Child Behavior Checklist profiles for children with OMS.

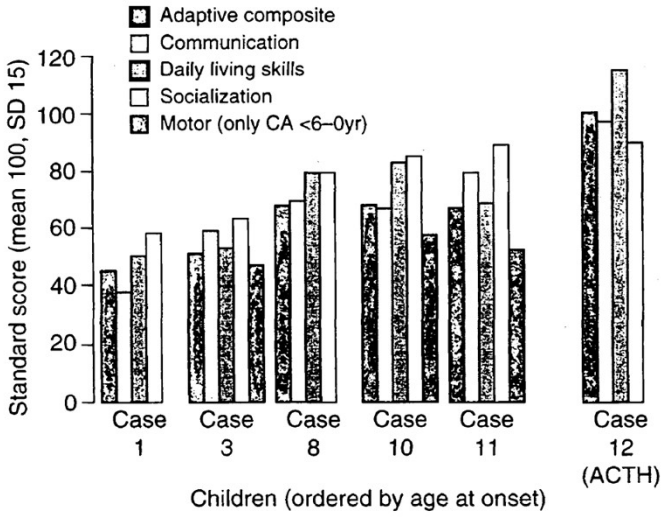
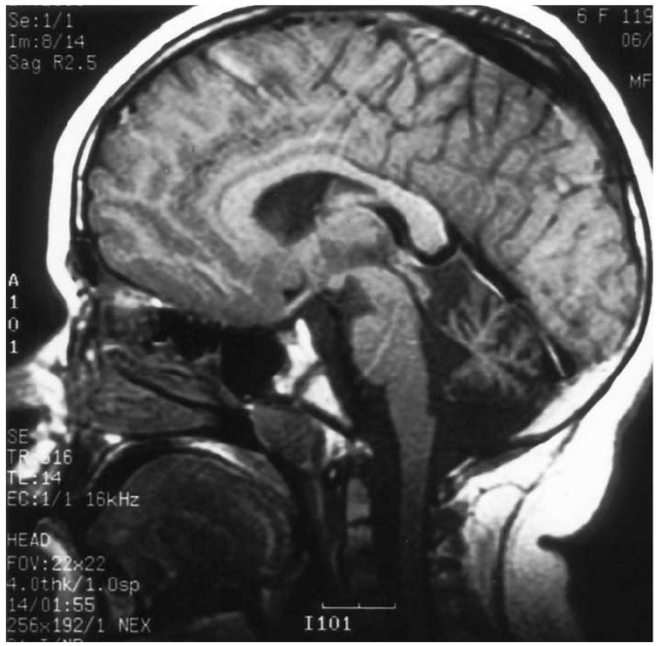


Fig. 3. Vineland Adaptive Behavior profiles (composite and domain scores) for children with OMS.

Behavioral trials

- Hayward et al 2001
  - OMAS patients identified through medical review, 11 evaluated at mean time of 7.6 years
  - Neurological, neurocognitive, dev/beh assessment, academic, MRI, serology
  - Measure: Child Behavior Checklist
  - Neurocog/behav/academic: 55% average range; 9% moderately below average; 36% severe cognitive and behavioral deficiencies
  - "Bimodal distribution": 5- "significant persistent functional morbidity" 5- "level of recovery allows them to function at a near-average in society"



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Behavioral trials

- Tate et al 2005
  - 105 individuals with OMAS recruited over 13 year period
  - OMA Parental Survey
  - 41% children in special education; 24% mainstream; 35% combination
  - Parents' biggest residual problem
    - 25% behavioral problems; 40% language impairment
  - 46% insomnia; 77% nighttime waking
  - Neuropsychiatric symptoms "in most children"
    - 58% obsessions/compulsions
    - 65% oppositional-defiant behavior
    - 79% rage attacks
    - 47% hyperactivity
    - 29% depression
    - 19% attention deficit

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Behavioral trials

- Turkel et al 2006
  - Children recruited from CHLA and parent-run support group, 17 children, 16 months to 12.5 years old
  - Neurological exam, psychiatric exam, Achenbach Child Behavior Checklist, Vineland
  - Persistent irritability, dysphoria, poor affective regulation in 10/17 by psychiatric assessment, 4/17 night terrors, disruptive behavior, aggression, SIB in 8/17; 4/15 elevated total score on Achenbach; clinically significant elevations in 8/15
    - 5/8: attention
    - 4/8: social problems
    - 3/8: thought problems
  - More behavioral problems noted on assessment then on parental report and significant supports needed for evaluation; more behavioral difficulties reported on Vineland than on Achenbach

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Behavioral trials

- De Grandis et al 2009
  - 14 subjects with localized neuroblastoma
  - Evaluated after median 7.8 years
  - Behavior/emotional assessments: Achenbach child behavior checklist
  - 10 evaluated with CBCL, 70% with pathological scores
    - 4- internalizing sx; 2-externalizing sx; 1-both
    - Only risk factor for behavioral problems was longer diagnostic delay
    - All patients with behavioral sequelae also had motor sequelae

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Neuropsychiatric features of OMAS

- Neurobehavioral
  - Insomnia
  - Irritability/inconsolability
  - “Rage attacks”
  - Impulsivity/Frontal-executive dysfunction
  - Social pragmatics deficits/Autism spectrum disorder symptoms/attenuated ASD-like symptoms
  - Chronic mood/anxiety symptoms
  - OCD-like or repetitive behavioral symptom profile
- Neurocognitive
  - Language (expressive>receptive)
  - Planning/executive
  - Working memory

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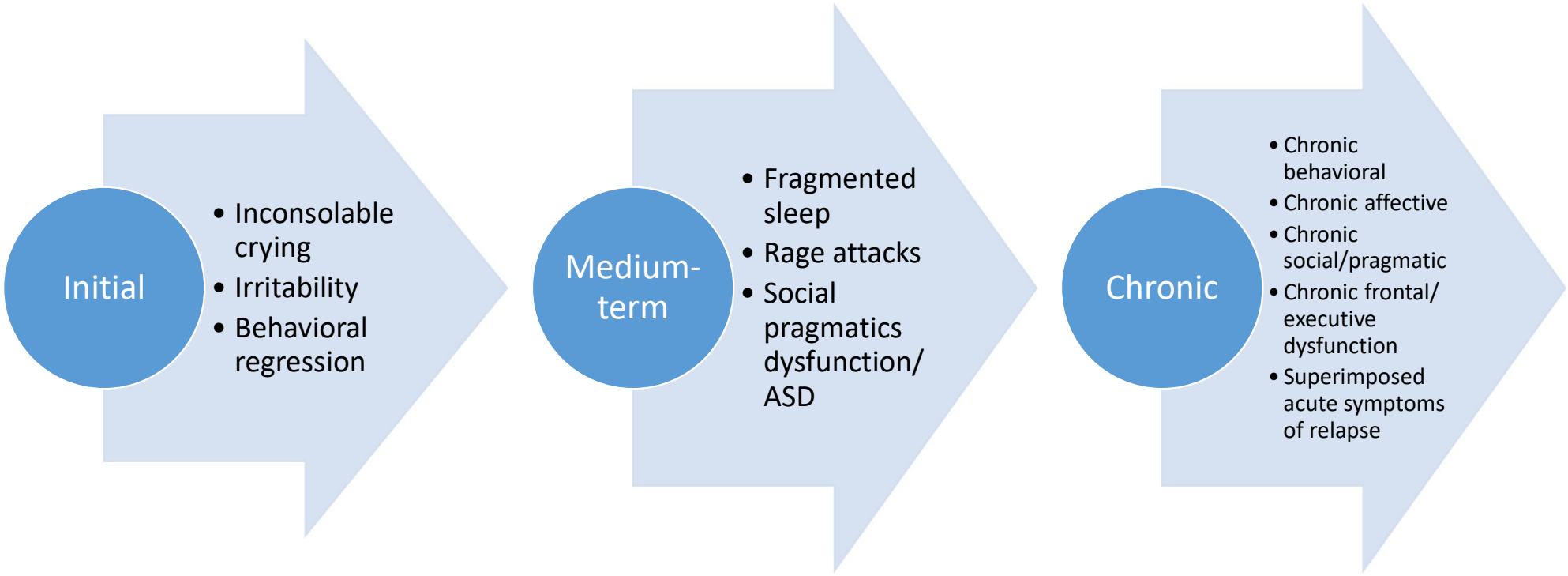
Time course



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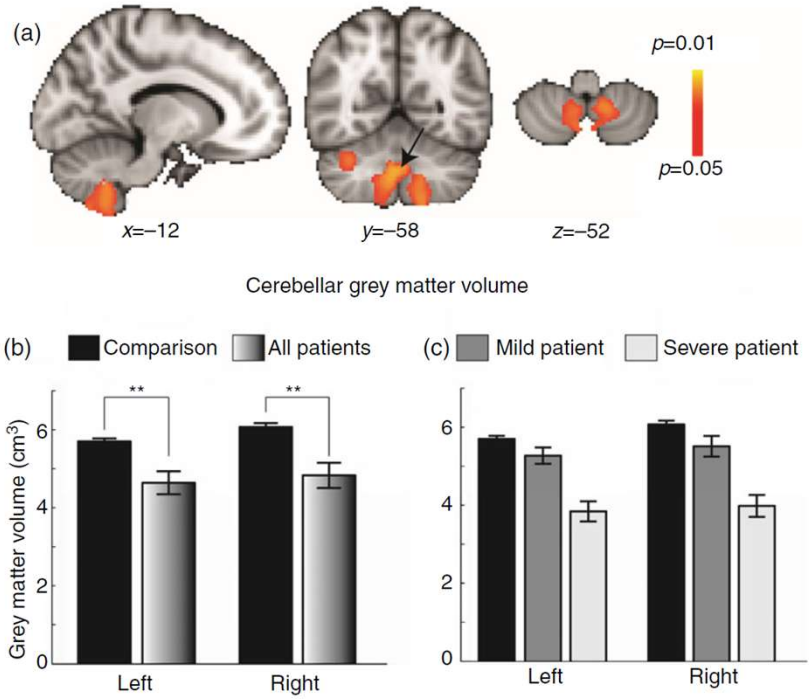
Neuroanatomy

- Cerebellar atrophy/gray matter loss
  - Vermis
  - Flocculonodular lobes
- Decreased white matter tract integrity
- Reduction in cerebral cortical thickness
  - Visual & motor areas
- Cerebellar gray matter volume loss corresponded with OMS severity score



Anand et al 2014

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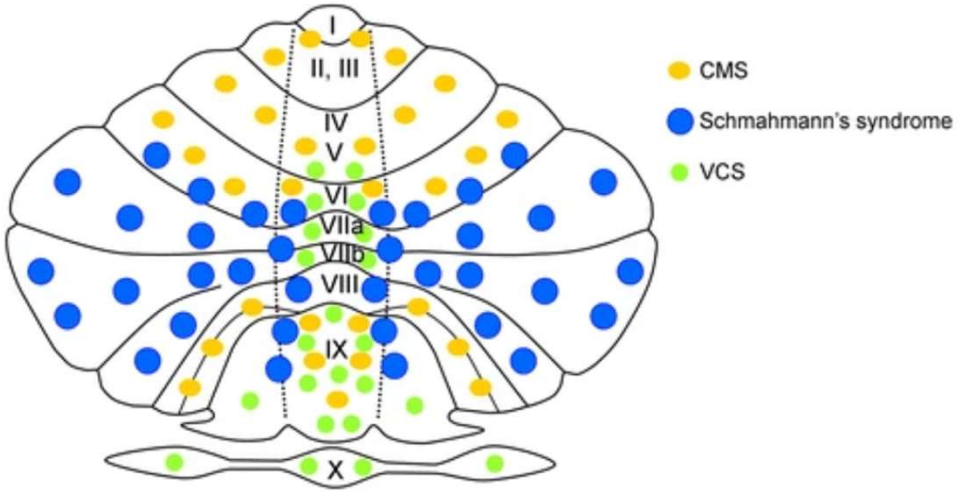
CCAS

- Turkel 2006, Stefanowicz 2008, Ohara 2007 mention cerebellar cognitive and affective syndrome (CCAS)
- Schmahmann 2021, Argyropoulos 2020 in the CCAS literature use OMAS as an example of a neuroinflammatory form of CCAS



Manto and Marien 2015

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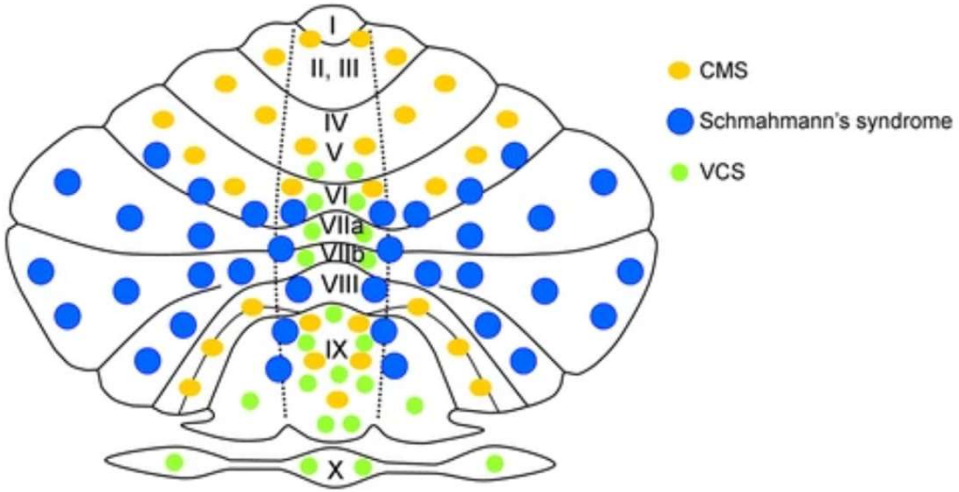
CCAS

- 1) executive deficits (deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency); mood, anxiety, manic-like symptoms
- 2) disruption of visuo-spatial cognition (visuo-spatial disorganization and impaired visuo-spatial memory)
- 3) personality changes (flattening or blunting of affect, and disinhibited or inappropriate behavior); autism-like syndrome, especially with younger-onset of injury
- 4) linguistic impairments (dysprosodia, agrammatism), mild anomia)



Manto and Marien 2015;
Taddei 2024

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Figure 2 The cerebellar cognitive affective/Schmahmann syndrome scale (Version 1A).

CEREBELLAR COGNITIVE AFFECTIVE / SCHMAHMANN SYNDROME SCALE (CCAS-Scale) VERSION 1A.

NAME: **DOB:**
ID# **Education (Yrs)**
DATE

		RAW SCORE	PASS=0 FAIL=1
SEMANTIC FLUENCY	Score = total correct words (up to a maximum of 26 words). Fail if Score 15 or less. *(Use space bottom right for notation).*		
Please name as many animals or living creatures as you can in one minute		/26	
PHONEMIC FLUENCY	Score = total correct words (up to a maximum of 19 words). Fail if Score 9 or less. *(Use space bottom right for notation).*		
Please name as many words as you can in one minute that start with the letter F. Do not use names of people or places or repeat the same word in different forms.		/19	
CATEGORY SWITCHING	Score = total number of correct alternating words (up to a maximum of 15 alternations). Repetitions or set loss errors are not scored. Fail if Score 9 or less. *(Use space bottom right for notation).*		
Please name a type of vegetable and then a type of profession or job, and then another vegetable and another profession, and so on, switching between the two lists. Name as many as you can in one minute.		/15	

Brain, Volume 141, Issue 1, January 2018, Pages 248–270, https://doi.org/10.1093/brain/awx317

Figure 2 The cerebellar cognitive affective/Schmahmann syndrome scale (Version 1A).

VERBAL REGISTRATION — This test is not scored. (The need for 4 attempts to learn 5 words raises concern for cerebral involvement).

I am going to read you a list of words which I would like you to learn. Please repeat these words. I am going to ask you to give them back in a few minutes. *(Read 5 words at rate of 1 / second. Subject repeats them once, then repeats them again. Repeat trials until subject recalls all 5 words. Stop after 4 attempts.)*

	[Flower]	[Robert]	[Courage]	[Speak]	[Yellow]
1st attempt	[ ]	[ ]	[ ]	[ ]	[ ]
2nd attempt	[ ]	[ ]	[ ]	[ ]	[ ]
3rd attempt	[ ]	[ ]	[ ]	[ ]	[ ]
4th attempt	[ ]	[ ]	[ ]	[ ]	[ ]

DIGIT SPAN FORWARD — Score = maximum string of numbers correctly repeated. Fail if Score 5 or less.

I am going to read you some numbers. Please repeat them in exactly the same order *(Read aloud at a rate of 1 per second. Start with * and administer previous items if subject fails to repeat *).*

5-9 [ ] 4-8-7-0 * [ ] 3-0-1-2-6-4 [ ] 2-0-5-6-9-7-3-8 [ ]
2-1-3 [ ] 1-6-9-2-5 [ ] 7-3-1-9-8-4-6 [ ]

/8

DIGIT SPAN BACKWARD — Score = maximum string of numbers correctly repeated. Fail if Score 3 or less. Inability to reverse 2 digits scores 0.

Now please say these numbers backwards, in reverse order. *(Give example, then start with *).*

(e.g., 5-8 = 8-5) *6-1 [ ] 3-8-2 [ ] 4-7-0-9 [ ] 6-5-2-8-1 [ ] 5-9-0-3-7-4 [ ]

/6

CUBE (DRAW) — Score = 15 points if 12 lines present and diagram is 3-dimensional. If 12 lines not present or the diagram is not 3 dimensional, administer "CUBE (COPY)".

Please draw a cube – a six-sided box, make it transparent or see-through. *(Use space bottom left).*

CUBE (COPY) — Score = 12 points, 1 for each line. Deduct 1 point if not 3-D, 1 point for each line not drawn, 1 point for each additional line >12. Fail if Score 11 or less.

Please copy the cube shown on PAGE 2. *(Neatness not scored).*

/15

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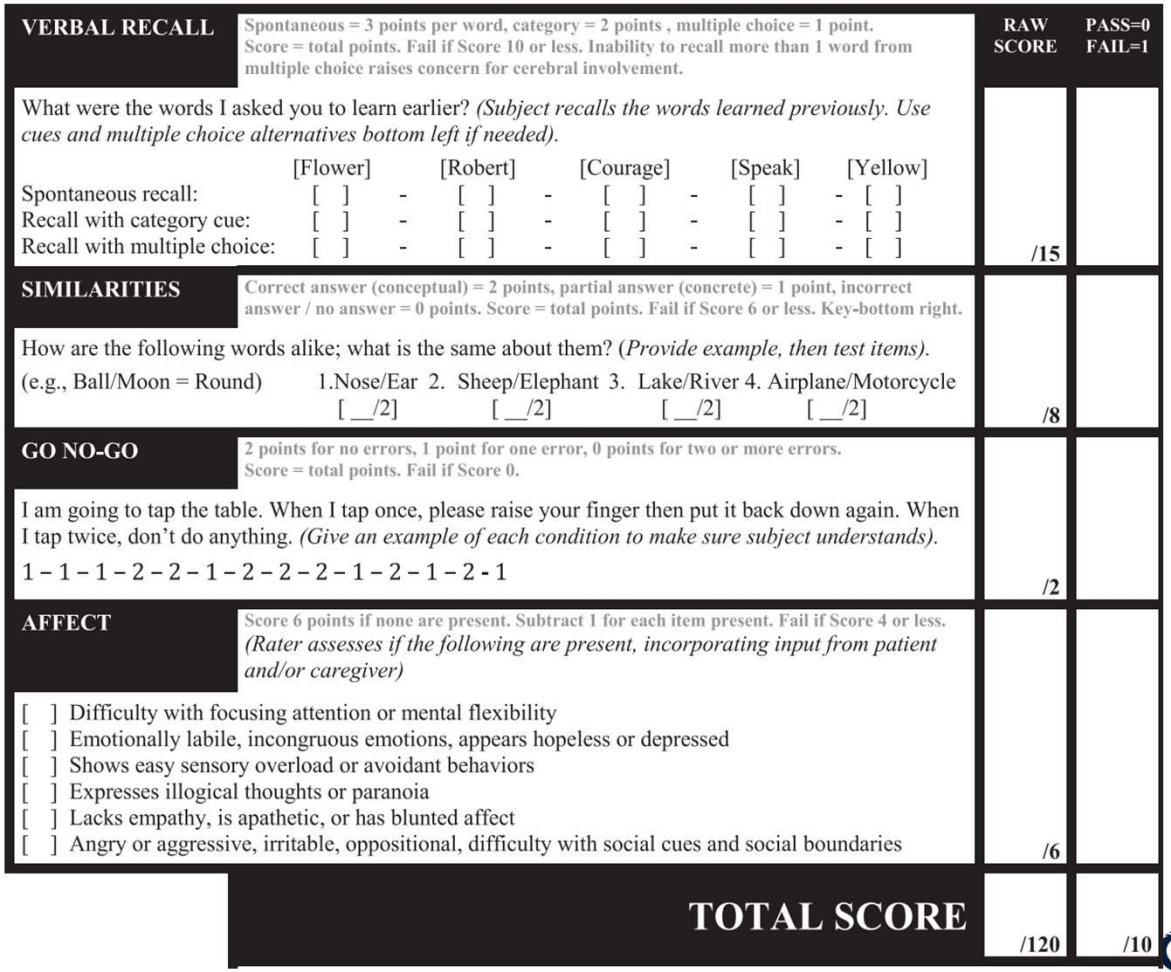
Figure 2 The cerebellar cognitive affective/Schmahmann syndrome scale (Version 1A).



		RAW SCORE	PASS=0 FAIL=1
VERBAL RECALL	Spontaneous = 3 points per word, category = 2 points , multiple choice = 1 point. Score = total points. Fail if Score 10 or less. Inability to recall more than 1 word from multiple choice raises concern for cerebral involvement.		
What were the words I asked you to learn earlier? *(Subject recalls the words learned previously. Use cues and multiple choice alternatives bottom left if needed).*			
	[Flower] [Robert] [Courage] [Speak] [Yellow]		
Spontaneous recall:	[ ] - [ ] - [ ] - [ ] - [ ]		
Recall with category cue:	[ ] - [ ] - [ ] - [ ] - [ ]		
Recall with multiple choice:	[ ] - [ ] - [ ] - [ ] - [ ]	/15	
SIMILARITIES	Correct answer (conceptual) = 2 points, partial answer (concrete) = 1 point, incorrect answer / no answer = 0 points. Score = total points. Fail if Score 6 or less. Key-bottom right.		
How are the following words alike; what is the same about them? (*Provide example, then test items).*			
(e.g., Ball/Moon = Round)	1.Nose/Ear [__/2] 2. Sheep/Elephant [__/2] 3. Lake/River [__/2] 4. Airplane/Motorcycle [__/2]	/8	
GO NO-GO	2 points for no errors, 1 point for one error, 0 points for two or more errors. Score = total points. Fail if Score 0.		
I am going to tap the table. When I tap once, please raise your finger then put it back down again. When I tap twice, don't do anything. *(Give an example of each condition to make sure subject understands).*			
1 – 1 – 1 – 2 – 2 – 1 – 2 – 2 – 2 – 1 – 2 – 1 – 2 - 1		/2	
AFFECT	Score 6 points if none are present. Subtract 1 for each item present. Fail if Score 4 or less. *(Rater assesses if the following are present, incorporating input from patient and/or caregiver)*		
[ ] Difficulty with focusing attention or mental flexibility			
[ ] Emotionally labile, incongruous emotions, appears hopeless or depressed			
[ ] Shows easy sensory overload or avoidant behaviors			
[ ] Expresses illogical thoughts or paranoia			
[ ] Lacks empathy, is apathetic, or has blunted affect			
[ ] Angry or aggressive, irritable, oppositional, difficulty with social cues and social boundaries		/6	
TOTAL SCORE		/120	/10

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Behavioral phenotypes

- Can we separate features of the pathophysiology of a disease from ancillary factors?
  - Permanent injury due to disease state
  - Transient, reversible injury due to inflammatory state, or other specific insult
  - Persistent symptomatology due to emotional trauma (illness, hospitalization, existential uncertainty, etc.)
    - Chronic PTSD
    - Family effects
  - Developmental impact of being a medically-ill child
  - Iatrogenic effects
    - Steroids, immunomodulatory agents

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Some challenges

- Idiosyncratic pharmacotherapies
  - Reliance on trazodone
- Unclear targets for medication treatment
  - Identifying underlying causes, such as PTSD versus ADHD versus CCAS
- Potential undertreatment of neuropsychiatric comorbidities due to lack of clear targets
- Limited ability to prognosticate given heterogenous endophenotypes
- Unclear guidance results in probable confusion and anxiety on parts of families
- Behavioral therapy challenges (forthcoming)

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Neuropsychology of OMAS

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Overview

- Cognitive symptoms of OMAS
  - Acute
  - Long-term
  - Challenges of assessment
- Case examples
- Cognitive takeaways
- Psychological interventions

Acute/subacute cognitive symptoms

- Limited focus on cognition at first presentation
  - Average age of patients
  - Prominence of behavioral symptoms
- Impact of acute sleep disruption on cognitive functioning, new learning

Long-term cognitive symptoms

- Literature is extremely variable, likely related to three main issues:
  - Sample size
  - Terminology: Cognitive = intellectual functioning vs. other domains of cognition
  - Variability in methodology/domain/instruments
  - Cohort effects

Long-term cognitive symptoms

- Study methodologies
  - Retrospective chart reviews (most)
    - Clinician-identified cognitive issues
    - Availability of neuropsychological data
  - Standardized data collection (cross-sectional, longitudinal)

Long-term cognitive symptoms

- Main cognitive domain assessed: IQ
- Full Scale IQ score is based on Spearman's g
  - General intelligence factor
  - Single mental ability that influences performance across most tasks

Long-term cognitive symptoms

Sheridan et al (2020)

- Combination retrospective chart review/prospective study (3 sites)
- 55 patients underwent cognitive testing (41 retrospective, 14 prospective)
  - WPPSI-III-R, WISC-IV, WAIS
  - FSIQ associated with multiphasic course, higher OMS severity score at last follow-up, failure to achieve remission, higher number of relapses
  - No association between FSIQ and sex, age at OMS onset, severity at presentation, tumor presence, time to first immunotherapy
  - Other cognitive and academic tests administered; results not provided

Long-term cognitive symptoms

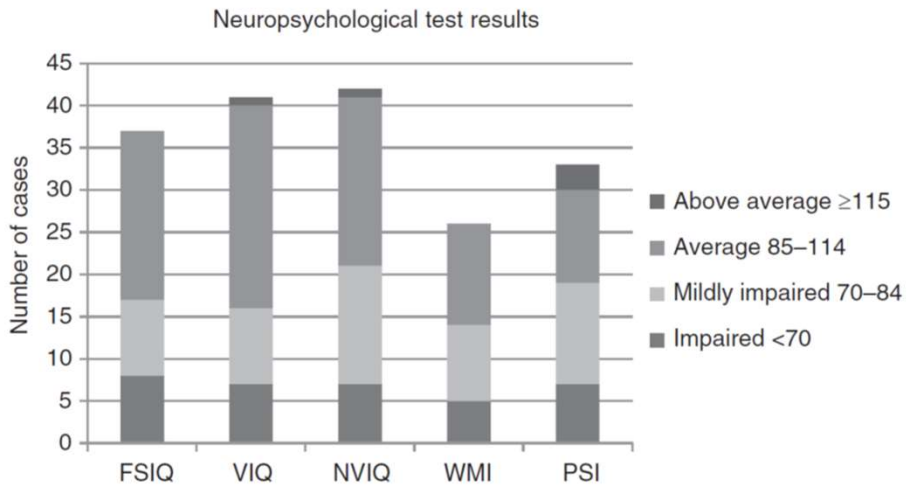


Figure 1: Neuropsychological test results classified by z-score in participants with normal pre-opsoclonus myoclonus syndrome development. FSIQ, full-scale IQ; VIQ, verbal IQ; NVIQ, non-verbal IQ; WMI, Working Memory Index; PSI, Processing Speed Index.

Sheridan et al (2020)

Long-term cognitive symptoms

Kumar et al (2024)

- Secondary aim: ANBL00P3 (OMAS with neuroblastoma)
- Study enrolled 53 patients under age 8 years
- Patients could be assessed at the time of diagnosis, 2 months, 6 months, and yearly until 10 years
  - Cognitive functioning measured using IQ (Bayley II, WPPSI-R, WISC-III/WISC-IV/WISC-V)
  - Adaptive functioning: Vineland Scales of Adaptive Behavior
- 25/53 patients with evaluable cognitive or adaptive data
  - Mean age at enrollment: 20.8 (SD 9.2)

Long-term cognitive symptoms

TABLE 4 Long-term cognitive functioning.

	Cognitive functioning						Age at neurocognitive assessment	
	N	Min	Max	Median	Mean	SD	Mean	Median
Diagnosis	15	50	109	78	81	18	21.0	17.3
2 Months	4	74	82	80	79	4	32.8	27.0
6 Months	5	50	102	84	80	22	23.8	25.5
1 Year	10	65	102	82	82	12	37.4	34.7
2 Years	5	67	82	72	75	7	49.4	49.5
3 Years	3	74	85	80	80	6	71.4	70.1
4 Years	6	85	101	91	92	6	74.5	72.5
5 Years	3	84	98	84	89	8	86.9	85.8
6 Years	3	83	103	92	93	10	98.2	96.7
7 Years	2	78	105	92	92	19	110.0	110.0
8 Years	0							
9 Years	2	57	66	62	62	6	132.8	132.8
10 Years	0							

Note: Time points are on the left, with cognitive scores for all patients with available data at each requested time point on the right. Minimum and maximum scores for all patients at each time point are included, along with the median and mean with standard deviation (SD). Mean and median ages of patients who completed evaluations at each time point are included on the right.

Kumar et al (2024)

Long-term cognitive symptoms

TABLE 2 Long-term adaptive functioning.

	Adaptive functioning						Age at neurocognitive assessment (months)	
	N	Min	Max	Median	Mean	SD	Mean	Median
Diagnosis	25	65	115	86	86	13	21.3	19.2
2 Months	13	57	108	90	86	16	24.2	23.3
6 Months	20	65	113	91	90	13	26.9	28.2
1 Year	17	35	118	84	80	21	35.7	32.9
2 Years	12	64	115	83	87	15	48.2	49.5
3 Years	9	76	114	93	95	14	59.4	55.0
4 Years	6	78	118	103	99	18	74.1	72.0
5 Years	6	70	111	94	94	15	90.1	88.9
6 Years	5	60	112	87	87	22	99.6	101.0
7 Years	2	80	111	96	96	22	114.9	114.9
8 Years	2	76	105	91	91	21	132.6	132.6
9 Years	0							
10 Years	1	71	71	71	71	–	147.0	147.0

Note: Time points are on the left, with Vineland scores for all patients with available data at each requested time point on the right. Minimum and maximum scores for all patients at each time point are included, along with the median and mean with standard deviation (SD). Mean and median ages of patients who completed evaluations at each time point are included on the right.

Kumar et al (2024)

Long-term cognitive symptoms

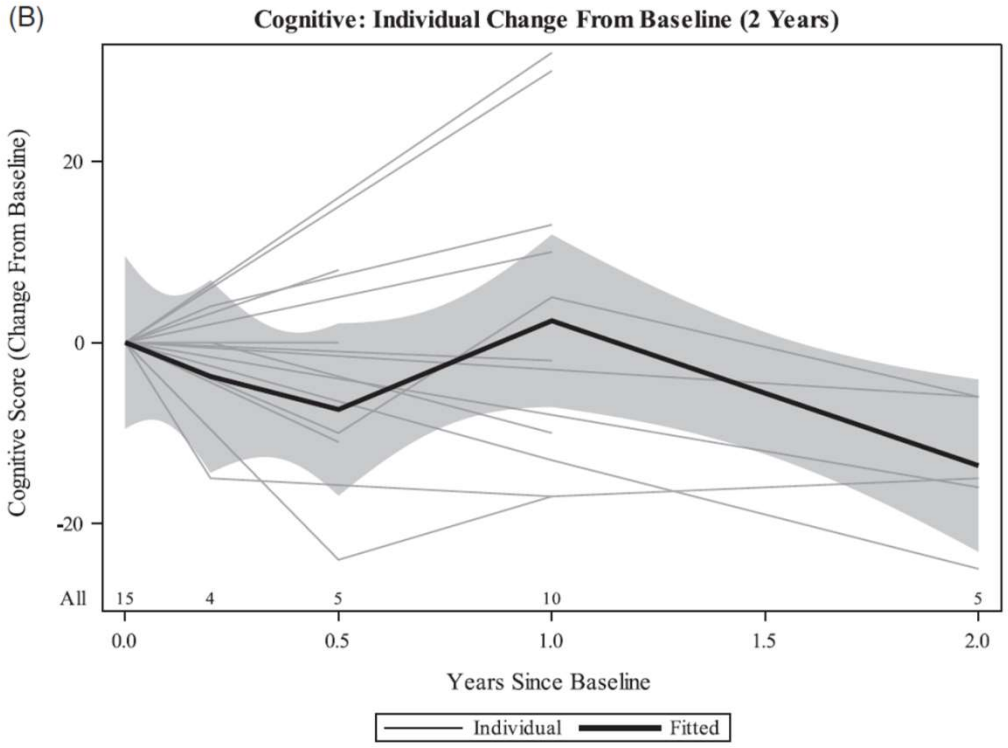


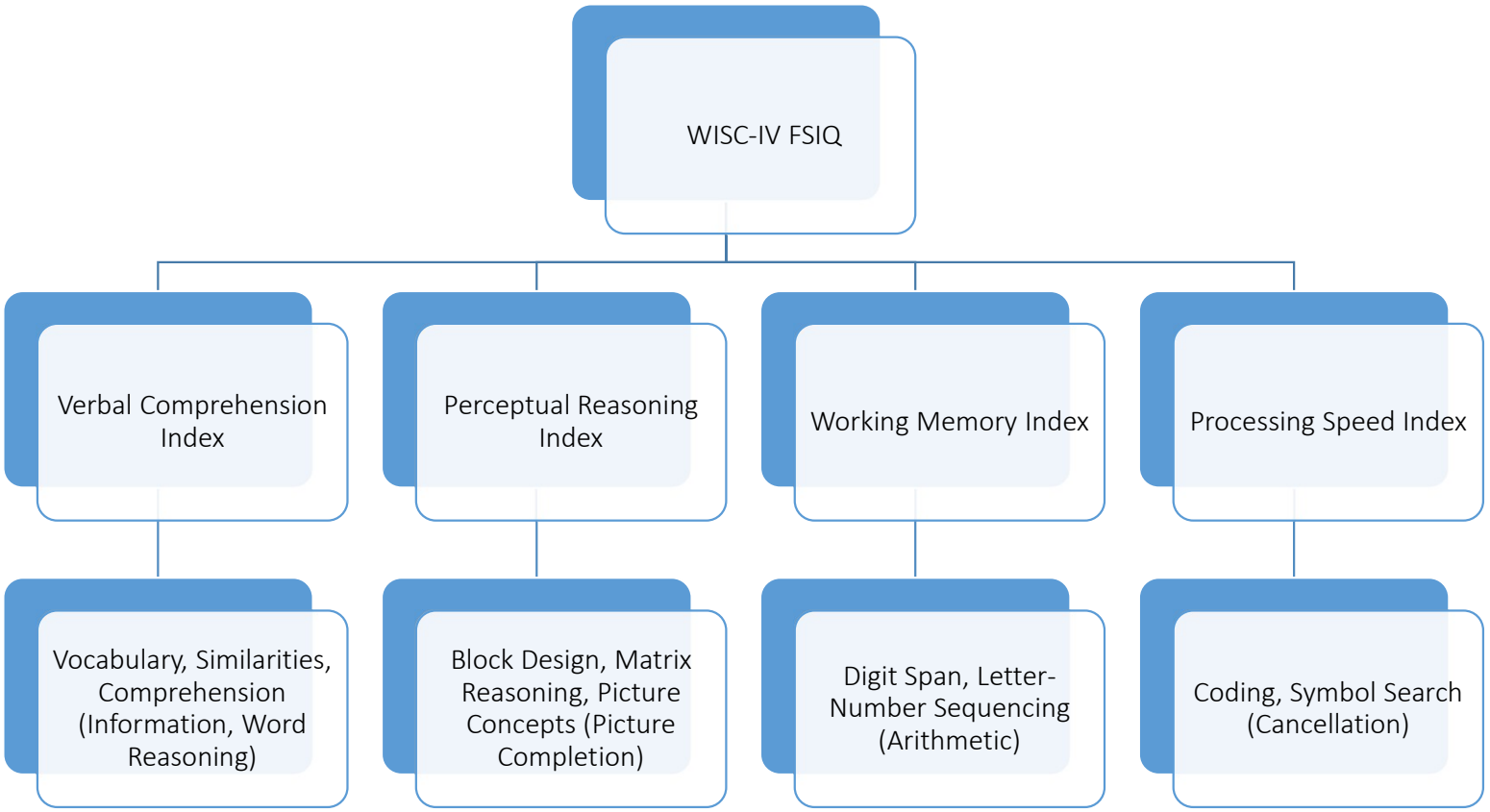
TABLE 3 Proportion of patients with clinically significant deficits.

	Cognitive functioning		Adaptive functioning	
	N	*N* (%) below 85	*N*	*N* (%) below 85
Diagnosis	15	8 (53)	25	12 (48)
2 Months	4	4 (100)	13	5 (38)
6 Months	5	3 (60)	20	7 (35)
1 Year	10	6 (60)	17	9 (53)
2 Years	5	5 (100)	12	7 (58)
3 Years	3	2 (67)	9	3 (33)
4 Years	6	0 (0)	6	2 (33)
5 Years	3	2 (67)	6	1 (17)
6 Years	3	1 (33)	5	2 (40)
7 Years	2	1 (50)	2	1 (50)
8 Years	0		2	1 (50)
9 Years	2	2 (100)	0	
10 Years	0		1	1 (100)

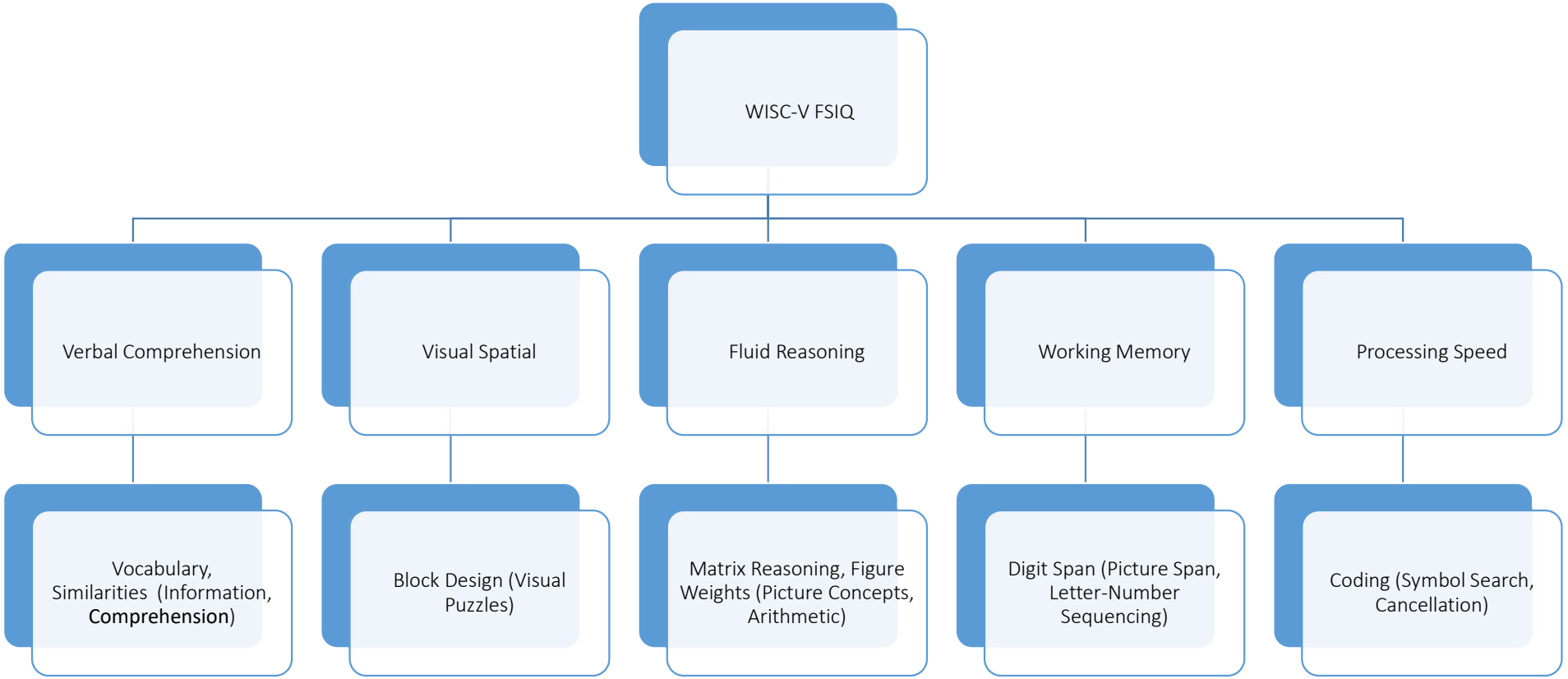
Note: The proportion of patients (with percentages) with clinically significant deficits (defined as score <85) for both adaptive function ($n = 25$) and cognitive function ($n = 15$) are shown in the columns to the right, with time points listed in the leftmost column.

Kumar et al (2024)

WISC-III to WISC-IV...

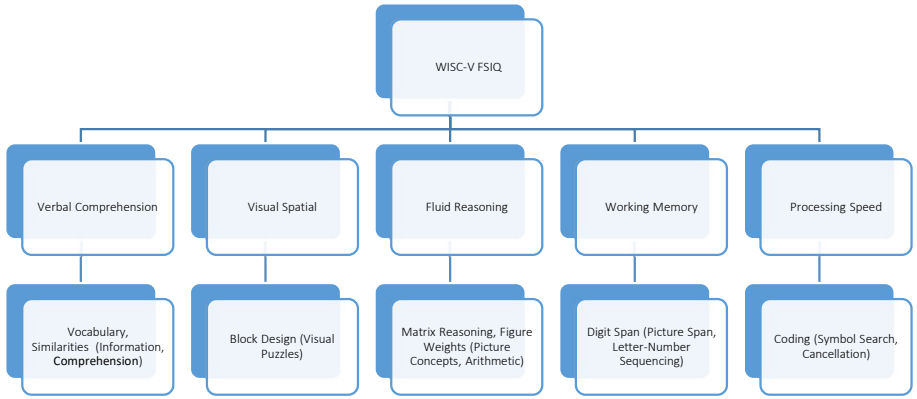


…WISC-IV to WISC-V



FSIQ Over Time: WISC-V

- FSIQ: 10 to 7 subtests
- 4 index scores to 5 domain scores
- 5 to 9 optional subtests
- Note: not all tests included from WISC-IV to WISC-V
- New tests added to WISC-V



FSIQ Over Time

- Changes in IQ composite score may mask true changes in cognition
- Composite IQ score may not capture "splinter skills"
- Impacted cognitive domains may not be captured in IQ measure
  - Attention
  - Motor coordination
  - Executive functioning

Cognitive Takeaways

- Consider differences in measures used over time
- Consider utility in overall IQ score as proxy for "cognition"
  - How to use FSIQ?
  - What else to consider? Domains? Subtests?
- Consider the meaning in variability
  - “Consistently inconsistent”
  - Understanding performance over time
  - Impact on functional performance and expectations

Psychological Interventions

- Behavioral
  - PCIT for younger kids and parents
  - PMT for older kids and parents
- Individual psychotherapy
  - Examples: CBT, TF-CBT, DBT/DBT-A
  - Emotion dysregulation and anxiety
  - Trauma-focused support for patients and families
- Providers may need to tailor therapies based on parent symptomatology, patient cognitive needs

Approaches based on other disorders

Can we find guidance from other diseases?

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TAND

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TSC-associated neuropsychiatric disorder

Table 1 Historical developments in TAND research

1880	TSC defined as a disorder of the brain [19]
1908	Description of the 'triad of impairment' which included seizures/epilepsy, intellectual disability and facial angiofibromas [20]
1911	The term 'epiloia' coined to describe epilepsy combined with 'anoia' (intellectual disability) in individuals with TSC [21]
1932	First descriptions of behaviours suggestive of autism, behavioural manifestations and different intellectual levels in individuals with TSC [22]
1967	First set of diagnostic criteria for TSC—not including any TAND manifestations or reference to seizures/epilepsy [23]
1983	First systematic research on behavioural aspects of TSC [24–26]
1987	Exploration of infantile spasms and its relationship with behavioural manifestations in TSC (e.g. autism, hyperkinetic behaviour, psychosis and aggression) [27]
1991	Consideration of neuropsychological deficits in TSC, in relation to memory, attention and executive functions [29]
1993	Further exploration of links between TSC and varied behavioural problems and identification of risk markers of behavioural manifestations [28]
1998	First International TSC Consensus Conference to develop revised diagnostic criteria and clinical management guidelines with little consideration of TAND [32, 33]
2005	TSC Behaviour Consensus Panel publish clinical guidelines for the assessment of cognitive and behavioural problems in TSC: recommendations of comprehensive assessment during all key developmental phases to identify emerging TAND and urgent assessment in case of sudden or unexpected change [36]
2007	Molecular hypothesis for the causes of TAND: the GRIPP hypothesis proposed that there is a direct molecular pathway from gene disruption to psychopathologies and that molecularly targeted treatments may reverse these deficits [42]
2008	First animal models of *TSC2*+/- showing reversal of learning deficits in response to mTORi [45]
2011	First human findings to show improvement in memory and executive deficits in humans with TSC after mTORi in an open-label trial [44]
2012	Second International TSC Consensus Conference to revise diagnostic criteria, as well as surveillance and treatment guidelines for TSC [8] The term 'TAND' was coined, and the recommendation was made to screen for TAND on an annual basis [9].
2012	Establishment of the TuberQus SClerosis registry to increase Awareness (TOSCA) consortium: the first large-scale international collaboration to study physical and TAND manifestations [49–51]
2015	Pilot validation and publication of the TAND Checklist [14, 17] with subsequent translation and authorisation in 19 languages (http://www.tandconsortium.org)
2016	Inclusion of TAND in Research Strategic Plan for TSC [52]
2017	First publication of randomised controlled trial findings on TAND from everolimus and sirolimus clinical trials [47]
2018	First description of natural TAND clusters [53]
2019	Launch of the TANDem project and establishment of the TAND consortium (http://www.tandconsortium.org)
2020	Replication of natural TAND clusters [54]
2021	Updated TSC Diagnostic Criteria and Surveillance and Management Recommendations including consensus guidelines for the identification and treatment of TAND [12]

GRIPP Global regulator and integrator of a range of physiological processes, *mTORi* Mechanistic target of rapamycin inhibitors, *TANDem* 'Empowering families through technology: a mobile-health project to reduce the TAND identification and treatment gap'

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TSC-associated neuropsychiatric disorder

- Long history of acknowledgement of neuropsychiatric symptoms of TSC (Vogt 1908)
  - "Triad of impairment" including seizures, ID, angiofibromas
- Consensus diagnostic criteria in 1998
- 2005 Clinical guidelines
- International TSC Consensus Conference 2012: Neuropsychiatry Panel recognized that though they were identified as part of guidelines, majority of neuropsychiatric symptoms were not identified or treated

2012 Second International TSC Consensus Conference to revise diagnostic criteria, as well as surveillance and treatment guidelines for TSC [8]
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TSC-associated neuropsychiatric disorder

- In response to emotional, behavioral, neurocognitive, and family-related concerns, "identification and treatment gap," and confusion in the international literature regarding neuropsychiatric and neurocognitive terminology, term TAND was coined in 2012
- Reported to have been coined because
  - Need for a "simple 'umbrella' term" that encompassed the heterogenous manifestations
  - "to provide a 'shared language' to define different levels of TAND"
- This facilitated creation of TAND checklist for healthcare screening and guidance

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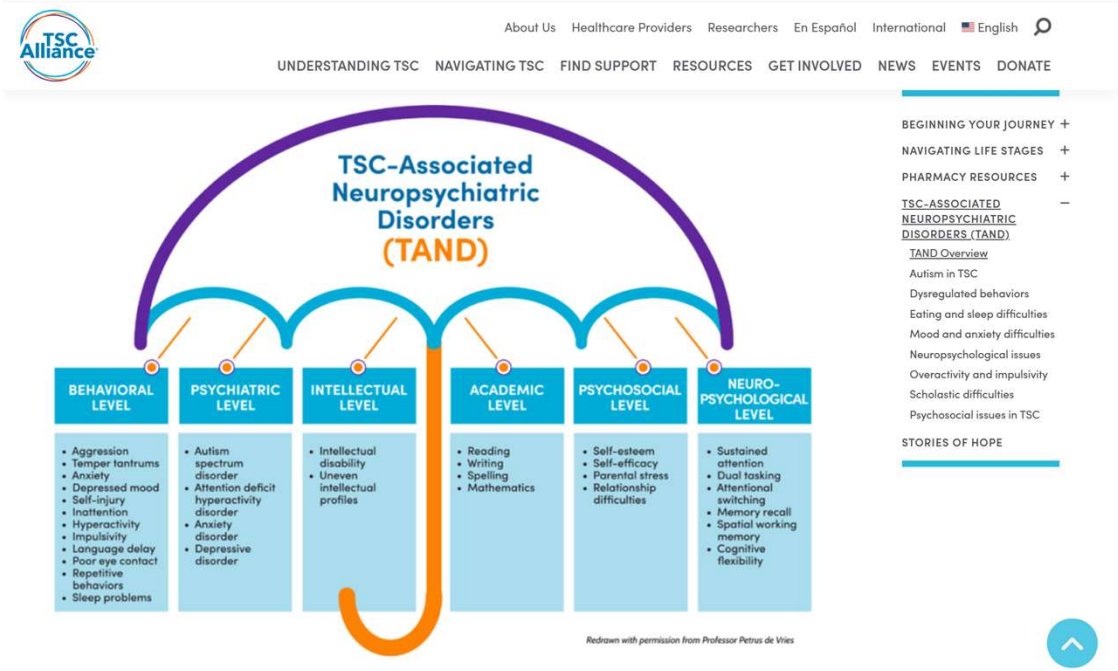
TSC-associated neuropsychiatric disorder

- Leclezio and deVries describe
  - 'treatment paralysis' due to 'overwhelming uniqueness of TAND profiles'
- Identified natural clusters of TAND manifestations following feasibility and replication studies on 453 participants
  - 7 TAND clusters: dysregulated behavior; scholastic; neuropsychological; overactive/impulsive; eat/sleep; mood/anxiety; ASD-like



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TSC-associated neuropsychiatric disorder

Table 2 The different levels of TAND

Level	Name	Description	Examples
Level 1	Behavioural level	This level includes all observed behaviours. The behavioural level is typically evaluated through direct observation or through a range of rating scale measures.	Aggression, anxiety, depressed mood, overactivity, impulsivity, poor eye contact, repetitive and ritualistic behaviours, sleep problems
Level 2	Psychiatric level	This level is defined by psychiatric diagnostic classification systems such as DSM-5 or ICD-11. At this level, the clinician determines whether behaviours observed at level 1 meet criteria for specific psychiatric disorders.	ADHD, autism, anxiety disorder, depressive disorder
Level 3	Intellectual level	This level measures intellectual ability as defined by standardised IQ-type measures.	Intellectual ability within the normal, mild, moderate, severe or profound range.
Level 4	Academic level	This level refers to specific learning disorders (as defined in DSM-5) associated with scholastic performance.	Reading, writing, spelling, or mathematics disorder.
Level 5	Neuropsychological level	This level examines specific brain-referenced systems through the use of standardised neuropsychological instruments.	Selective, sustained or dual-tasking attention deficits; unilateral neglect; immediate recall memory deficits; spatial working memory deficits; visuo-spatial deficits; executive deficits
Level 6	Psychosocial level	This level explores the psychological and social impact of TSC in terms of self, family and community relationships.	Low self-esteem, low self-efficacy, high family stress, parental relationship difficulties, community stigma and isolation

DSM-5 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [59], *ICD-11* International Classification of Diseases and Related Health Problems, Eleventh Edition [60]

TAND clusters	TAND items
1. Scholastic	Reading, writing, spelling, mathematics
2. Neuropsychological	Memory, disorientation, attention deficits (behavioural and neuropsychological), visuo-spatial deficits, dual-task deficits, executive function deficits
3. Dysregulated behaviour	Aggressive outbursts, temper tantrums, self-injury
4. Overactive/impulsive	Overactivity, impulsivity, restlessness
5. Eat/sleep	Eating difficulties, sleep difficulties
6. Mood/anxiety	Anxiety, depressed mood, extreme shyness, mood swings
7. Autism spectrum disorder–like	Inflexibility, unusual language, delayed language, repetitive behaviours, poor eye contact, peer difficulties

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Is TSC unique?

- Paying attention and concentrating (61.9%)
- Impulsivity (54.8%)
- Temper tantrums (54.8%)
- Anxiety (45.2%)
- Overactivity/hyperactivity (40.5%)
- Aggressive outburst (40.5%)
- Absent or delayed onset of language (40.5%)
- Repetitive behaviors (35.7%)
- Academic difficulties (>40%)
- Deficits in attention (61.9%)
- Executive skills (50%)

TSC data

1. Paying attention and concentrating (59.5%)
2. Impulsivity (52.4%)
3. Anxiety (50%)
4. Overactivity/hyperactivity (38.1%)
5. Temper tantrums (38.1%)
6. Academic difficulties (>40%)
7. Deficits in attention (59.5%)
8. Executive skills (38.1%)

NF1 data

2020 Cervi

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Is TSC unique?

- FXAND: proposed in 2018 by Hagerman et al "to promote research and the use of fragile X DNA testing to enhance recognition and treatment for these disorders."
    - Focus is on FrX premutation carriers who are at elevated risk for ADHD, ASD, anxiety, depression, SPCD, etc

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Clinical anecdotes

- Anecdotally:
  - Aaron's TSC referrals: I see many children and families related to a broad range of complex neurogenetic and acquired conditions. TAND is one of the few for which I get a specific screening and treatment request

  - Hannah's NF1 referrals: Disparity in testing numbers, data acquisition, and recommendations for NF1 referrals based on there being clear guidelines and specialized care providers focused in that area

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Products of this terminology

- Note dramatic increase in studies following terminological change

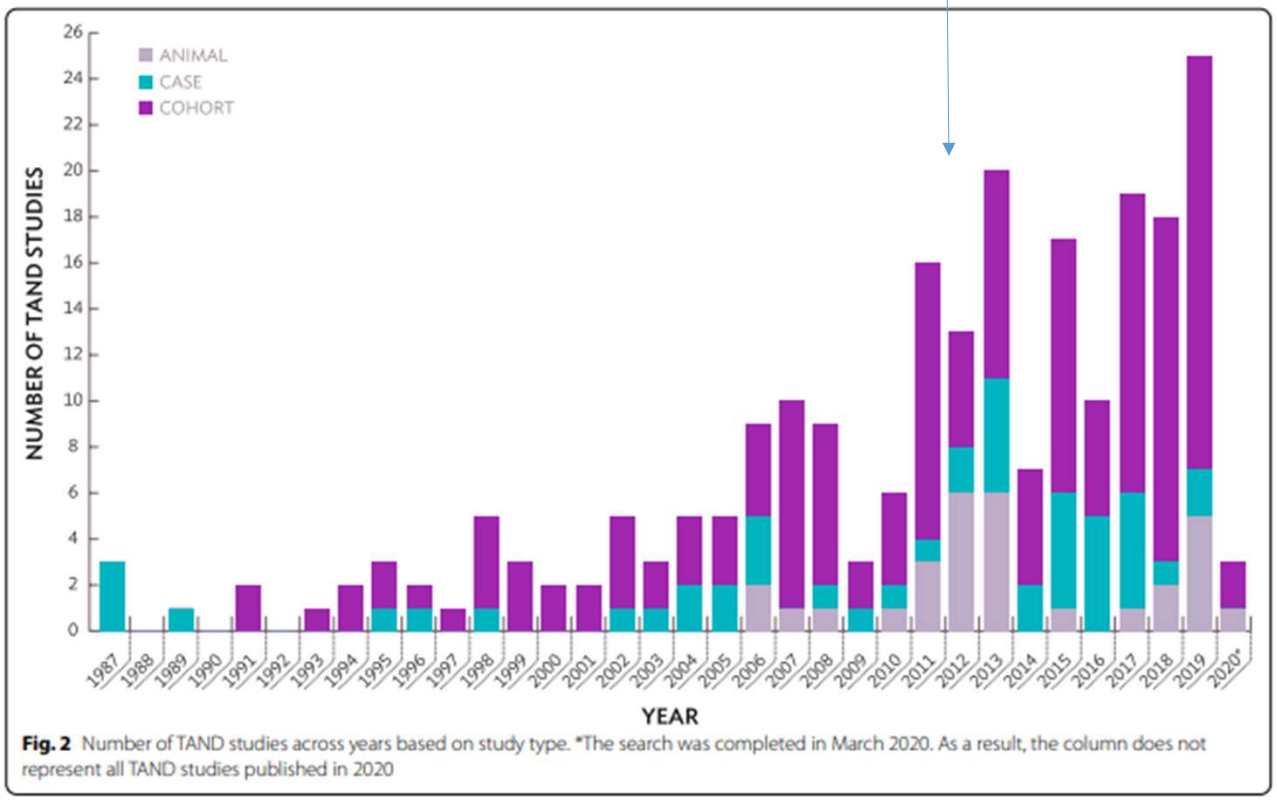

Fig. 2 Number of TAND studies across years based on study type. *The search was completed in March 2020. As a result, the column does not represent all TAND studies published in 2020

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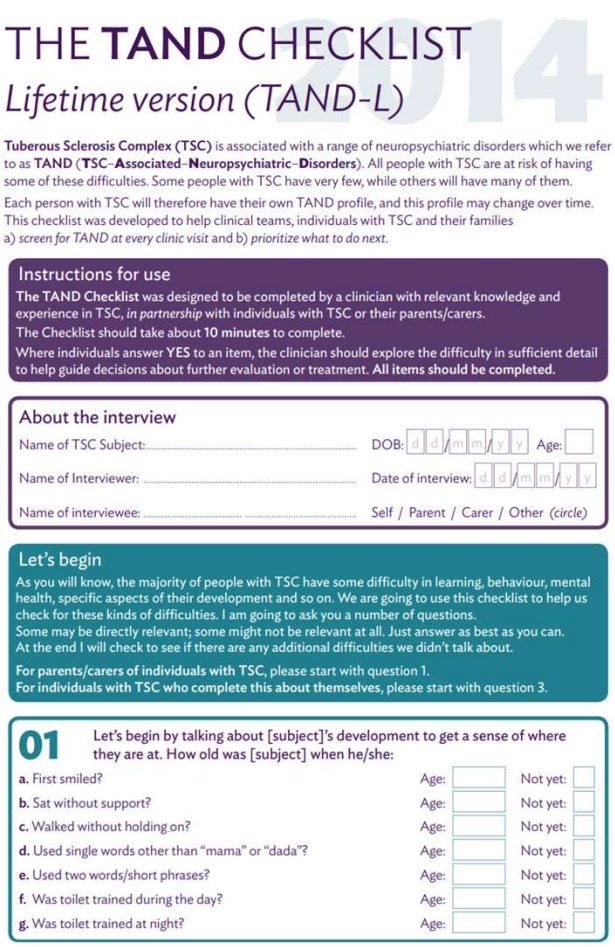
Products of this terminology



THE **TAND** CHECKLIST 2014

Lifetime version (TAND-L)

Tuberous Sclerosis Complex (TSC) is associated with a range of neuropsychiatric disorders which we refer to as **TAND** (**TSC-Associated-Neuropsychiatric-Disorders**). All people with TSC are at risk of having some of these difficulties. Some people with TSC have very few, while others will have many of them.

Each person with TSC will therefore have their own TAND profile, and this profile may change over time. This checklist was developed to help clinical teams, individuals with TSC and their families a) *screen for TAND at every clinic visit* and b) *prioritize what to do next*.

Instructions for use

The TAND Checklist was designed to be completed by a clinician with relevant knowledge and experience in TSC, *in partnership* with individuals with TSC or their parents/carers.

The Checklist should take about **10 minutes** to complete.

Where individuals answer **YES** to an item, the clinician should explore the difficulty in sufficient detail to help guide decisions about further evaluation or treatment. **All items should be completed.**

About the interview

Name of TSC Subject: ..... DOB: d d / m m / y y Age:

Name of Interviewer: ..... Date of interview: d d / m m / y y

Name of interviewee: ..... Self / Parent / Carer / Other *(circle)*

Let's begin

As you will know, the majority of people with TSC have some difficulty in learning, behaviour, mental health, specific aspects of their development and so on. We are going to use this checklist to help us check for these kinds of difficulties. I am going to ask you a number of questions.
Some may be directly relevant; some might not be relevant at all. Just answer as best as you can.
At the end I will check to see if there are any additional difficulties we didn't talk about.

For parents/carers of individuals with TSC, please start with question 1.
For individuals with TSC who complete this about themselves, please start with question 3.

01 Let's begin by talking about [subject]'s development to get a sense of where they are at. How old was [subject] when he/she:

a. First smiled?	Age:	Not yet:
b. Sat without support?	Age:	Not yet:
c. Walked without holding on?	Age:	Not yet:
d. Used single words other than "mama" or "dada"?	Age:	Not yet:
e. Used two words/short phrases?	Age:	Not yet:
f. Was toilet trained during the day?	Age:	Not yet:
g. Was toilet trained at night?	Age:	Not yet:

02 What is [subject]'s current level of *(please tick)*:

a. Language:	non-verbal	simple language	fluent
b. Self-care:	dependent on others	some self-care skills	independent
c. Mobility:	wheelchair	needs significant support	some difficulty	completely mobile

03 Let's talk about behaviours causing concern to you or to other people. Have/has [subject] ever had difficulty with any of the following?

a. Anxiety	NO	YES
b. Depressed mood	NO	YES
c. Extreme shyness	NO	YES
d. Mood swings	NO	YES
e. Aggressive outbursts	NO	YES
f. Temper Tantrums	NO	YES
g. Self-injury, such as hitting self, biting self, scratching self	NO	YES
h. Absent or delayed onset of language to communicate	NO	YES
i. Repeating words or phrases over and over again	NO	YES
j. Poor eye contact	NO	YES
k. Difficulties getting on with other people of similar age	NO	YES
l. Repetitive behaviours, *such as doing the same thing over and over again*	NO	YES
m. Very rigid or inflexible about how to do things or not liking change in routines	NO	YES
n. Overactivity/hyperactivity, *such as being constantly on the go*	NO	YES
o. Difficulty paying attention or concentrating	NO	YES
p. Restlessness or fidgetiness, *such as wriggling or squirming*	NO	YES
q. Impulsivity, *such as butting in, not waiting turn*	NO	YES
r. Difficulties with eating, *such as eating too much, too little, unusual things*	NO	YES
s. Sleep difficulties, *such as with falling asleep or waking*	NO	YES
If you answered YES to any of the above:		
Have you had further evaluation or support for it?	NO	YES
Would you like to have further evaluation or support for it?	NO	YES

04 Problem behaviours may add up to meet criteria for specific psychiatric disorders. Have/has [subject] ever received a diagnosis of:

a. Autism Spectrum Disorder (ASD), *including autism, Asperger's*	NO	YES
b. Attention Deficit Hyperactivity Disorder (ADHD)	NO	YES
c. Anxiety Disorder, *including as panic, phobia, separation anxiety disorder*	NO	YES
d. Depressive Disorder	NO	YES
e. Obsessive Compulsive Disorder	NO	YES
f. Psychotic Disorder, *including schizophrenia*	NO	YES
If you answered YES to any of the above		
Have you had further evaluation or support for it?	NO	YES
Would you like to have further evaluation or support for it?	NO	YES

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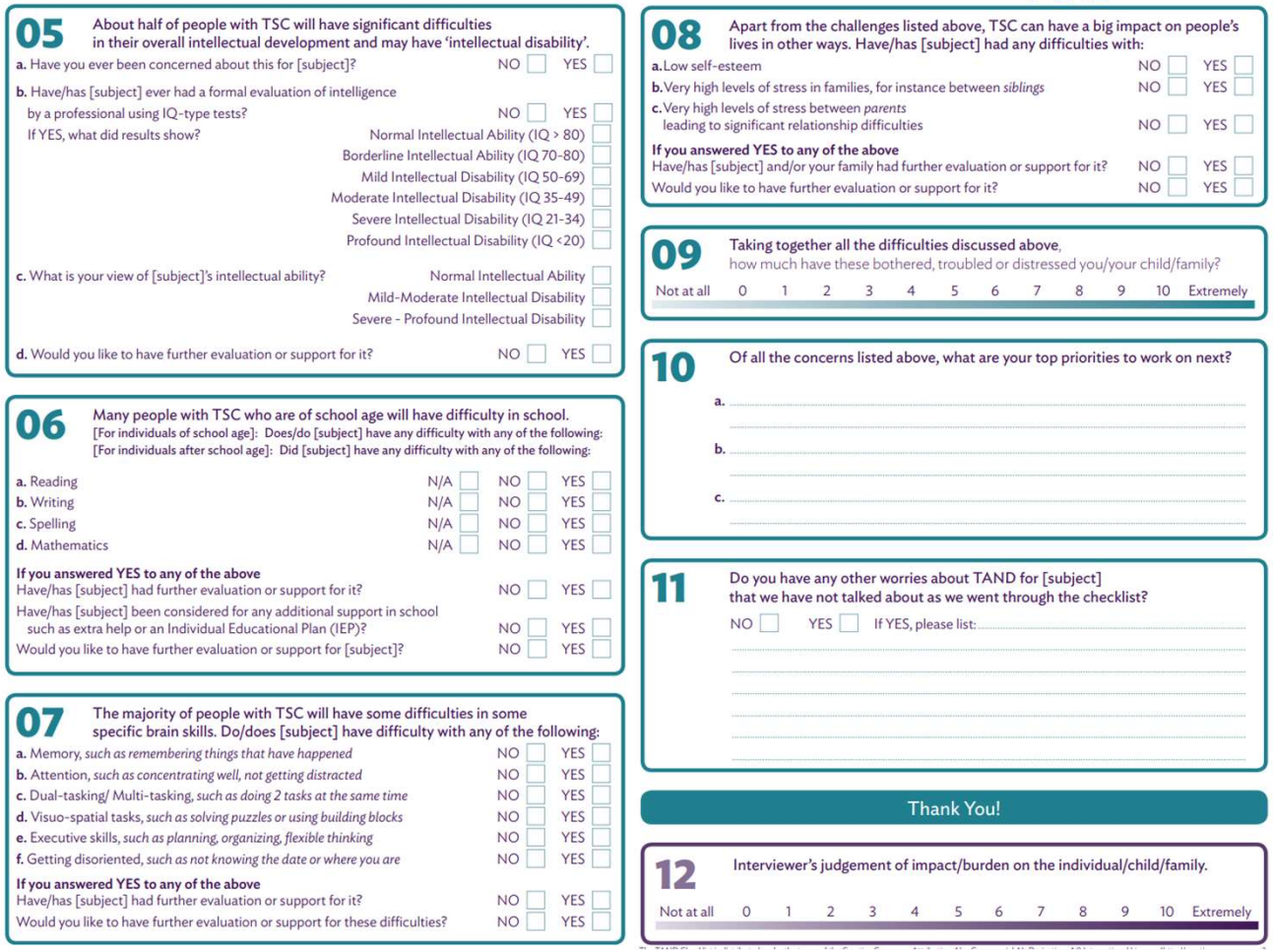
Products of this terminology



05 About half of people with TSC will have significant difficulties in their overall intellectual development and may have 'intellectual disability'.

a. Have you ever been concerned about this for [subject]? NO ☐ YES ☐

b. Have/has [subject] ever had a formal evaluation of intelligence by a professional using IQ-type tests? NO ☐ YES ☐

If YES, what did results show?
- Normal Intellectual Ability (IQ > 80) ☐
- Borderline Intellectual Ability (IQ 70-80) ☐
- Mild Intellectual Disability (IQ 50-69) ☐
- Moderate Intellectual Disability (IQ 35-49) ☐
- Severe Intellectual Disability (IQ 21-34) ☐
- Profound Intellectual Disability (IQ <20) ☐

c. What is your view of [subject]'s intellectual ability?
- Normal Intellectual Ability ☐
- Mild-Moderate Intellectual Disability ☐
- Severe - Profound Intellectual Disability ☐

d. Would you like to have further evaluation or support for it? NO ☐ YES ☐

06 Many people with TSC who are of school age will have difficulty in school.
[For individuals of school age]: Does/do [subject] have any difficulty with any of the following:
[For individuals after school age]: Did [subject] have any difficulty with any of the following:

	N/A	NO	YES
a. Reading	☐	☐	☐
b. Writing	☐	☐	☐
c. Spelling	☐	☐	☐
d. Mathematics	☐	☐	☐

If you answered YES to any of the above
Have/has [subject] had further evaluation or support for it? NO ☐ YES ☐
Have/has [subject] been considered for any additional support in school such as extra help or an Individual Educational Plan (IEP)? NO ☐ YES ☐
Would you like to have further evaluation or support for [subject]? NO ☐ YES ☐

07 The majority of people with TSC will have some difficulties in some specific brain skills. Do/does [subject] have difficulty with any of the following:

	NO	YES
a. Memory, *such as remembering things that have happened*	☐	☐
b. Attention, *such as concentrating well, not getting distracted*	☐	☐
c. Dual-tasking/ Multi-tasking, *such as doing 2 tasks at the same time*	☐	☐
d. Visuo-spatial tasks, *such as solving puzzles or using building blocks*	☐	☐
e. Executive skills, *such as planning, organizing, flexible thinking*	☐	☐
f. Getting disoriented, *such as not knowing the date or where you are*	☐	☐

If you answered YES to any of the above
Have/has [subject] had further evaluation or support for it? NO ☐ YES ☐
Would you like to have further evaluation or support for these difficulties? NO ☐ YES ☐

08 Apart from the challenges listed above, TSC can have a big impact on people's lives in other ways. Have/has [subject] had any difficulties with:

	NO	YES
a. Low self-esteem	☐	☐
b. Very high levels of stress in families, for instance between *siblings*	☐	☐
c. Very high levels of stress between *parents* leading to significant relationship difficulties	☐	☐

If you answered YES to any of the above
Have/has [subject] and/or your family had further evaluation or support for it? NO ☐ YES ☐
Would you like to have further evaluation or support for it? NO ☐ YES ☐

09 Taking together all the difficulties discussed above, how much have these bothered, troubled or distressed you/your child/family?

Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely

10 Of all the concerns listed above, what are your top priorities to work on next?

a. .....
b. .....
c. .....

11 Do you have any other worries about TAND for [subject] that we have not talked about as we went through the checklist?

NO ☐ YES ☐ If YES, please list: .....

Thank You!

12 Interviewer's judgement of impact/burden on the individual/child/family.

Not at all 0 1 2 3 4 5 6 7 8 9 10 Extremely

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OMASAND?

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Recap, Summary and Possible Deliverables

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Goals

- Better characterize the cognitive, emotional and behavioral endophenotype(s) of OMAS
- Codify Neuropsychiatric Treatment and Neuropsychological Testing recommendations
- Provide guidance that will be usable outside of tertiary care academic settings
- Determine specific therapeutic intervention recommendations

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Goals

- Better characterize the cognitive, emotional and behavioral endophenotype(s) of OMAS
  - What are the needs of patients and families?
  - What are the prescribing habits of providers?
  - What are the psychiatric and behavioral outcomes at different phases of illness?
  - What are unmet needs in the behavioral healthcare of individuals with OMAS and their families?
  - Who is best situated to contribute to this characterization?
  - Neuropsychology/Neuropsychiatry task force?

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Goals

- Codify Neuropsychiatric Treatment and Neuropsychological Testing recommendations
  - Identify recommended assessment domains and protocolize neuropsychological and psychoeducational testing recommendations (battery, frequency, recommendations)
  - Provide recommendation for serial testing and monitoring
  - Discuss the concept of "growing into" one's disease profile, what is challenging at different phases, and how does this pertain specifically to developmentally appropriate OMAS monitoring

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Possible Next Steps

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Summary

- Identify stakeholders
  - Who would take part in task force?
  - When/how to involve families and impacted individuals?
- Publish existing data
  - Make literature available regarding neuropsychiatric findings that are considered “common knowledge”
- Determine most relevant, next research steps
  - Publish case-series and small studies utilizing existing data
  - Survey-based research modeled on recent sleep study
- Push out consensus recommendations for neuropsychiatric evaluation, neuropsychiatric care, and specific therapeutic interventions
  - Are we there yet? What else do we need?
- Determine key clinician/researchers who can contribute to Neuropsychiatric Consensus Statement

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Goals for guidelines- Referring Providers

- Which members should the multidisciplinary team consist of
- Whom should patients be referred to at each phase of illness, and with what frequency
- What are outcomes or data points that providers should be aware of for monitoring and reassessment
- What data exists to inform families about potential outcomes and trajectory
- What services may be needed and what should primary team work to facilitate?
    - E.g., as guardianship, developmental disabilities services, SSI/SSDI,
    - When do you get social work or case management assistance?

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Goals for guidelines- Neuropsychology

- Expected neuropsychological profiles, complex topography, and the limits of FSIQ
- Frequency of re-evaluation recommendations (with particular focus on guidance that can be used for insurance justification)
- What are important neurocognitive domains of focus? What will help us work towards standardization?
- Salience of timing: considering testing in the context of different illness phases
  - E.g., the impact of acute and long-term steroid treatments, and potential impact of other agents on testing
  - Impact of neurobehavioral symptoms, sleep, and other comorbidities on testing, and potential benefit of treatment (e.g., ADHD) before testing

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Goals for guidelines- Psychiatry/ Neuropsychiatry

- Clearly publicizing known neurobehavioral and comorbidity profile at each disease phase
- Importance of addressing sleep
- Utility in aggressive management of executive function and emotional regulation/lability
- Crucial nature of addressing individual and family trauma experience such as hypervigilant parental responsiveness
    - Oncology analogue: “you have to parent your child through their treatment like they’re not always going to have cancer”
- Necessity of appropriate utilization of other interventions such as targeted SLP/OT (for social pragmatics, not just motor skills), Child Parent Psychotherapy, specific Cognitive Behavioral Therapies, etc.
- Determine potential comorbidities that have their own specific treatments, such as anxiety, PTSD, ADHD and address these unique comorbidities with targeted interventions

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Goals for guidelines- Behavioral Providers

- Focus on parental behavioral interventions during younger years, and then child-focused interventions as individuals age
    - E.g., PCIT, CPP, PMT early on, and then social pragmatics skills building and behavioral training with focus on role-playing and in vivo practice, as for ASD and ADHD protocols
- Cognitive-rehabilitation and executive function skills training for the child themselves
- Integrate an understanding of the individual's cognitive status and neuropsychological profile to be able to appropriately adapt therapy
    - e.g., use brief x-y statements, utilize visual aides, immediate behavioral reinforcement, etc.

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Goals for guidelines- Family Guidance

- Messaging about, and interventions regarding, behaviors even during acute phase of OMAS
  - Behaviors can be addressed regardless of cause
  - Feelings are OK, but actions may not be
  - PMT/behavioral strategies can be effective regardless of symptom cause
  - The acute phase will not always be the acute phase
  - Interventions can begin even during treatment, for example providing initial behavioral interventions during IVIg

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Goals for guidelines- Family Guidance

- Motor symptoms usually get better; behavioral and cognitive ones have a more confusing and variable time course
- Motor symptoms often improve because we utilize numerous interventions – disease-modifying medication, symptomatic medication, PT, OT, ST, etc. Patients get multimodal motor interventions, what are they getting for behavioral and emotional symptoms? Highlighting benefits seen in multimodal motor symptom management may get traction on behavioral and emotional care
- Cognitive, emotional, and behavioral symptoms are very real, core parts of OMAS. During acute phase, often viewed as less important, or that it will “get better,” but we often see the opposite

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Goals for guidelines- Family Guidance

- Families need care for medical trauma, which is common in such complex, frightening illness
- Kids may have their own complex experiences of their illness, which should be understood, talked about, and, if appropriate, addressed

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