

Guidelines for the assessment of cognitive and behavioural problems in Tuberous Sclerosis: assessments needed in TSC, when to do them, and recommended tests

*"...behavioural disorders are underrecognised, underdiagnosed and often not treated in TSC"
Behavioral and Psychiatric Panel, NIH TSC Consensus Conference, Annapolis USA, 1998*

Tuberous sclerosis (TSC) is a multi-system genetic disorder caused by mutations in the tumour suppressor genes, *TSC1* or *TSC2* and is characterised by abnormal growths in a wide range of organs including the skin, kidneys and central nervous system. In over two-thirds of cases diagnosis is made when an infant presents with epileptic seizures in the first year of life. In the brain, features include cortical tubers (CT), subependymal nodules (SEN), subependymal giant cell astrocytomas (SEGA) and widespread grey and white matter abnormalities. Intractable epilepsy is a major medical concern to doctors, but less attention is paid to the behavioural and neuropsychiatric problems also associated with TSC such as Autism Spectrum Disorders (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) which are often of greater concern to families. It is a worldwide feature that there is often little or no clinical assessment or intervention offered for problems in these areas, in spite of the fact that these can lead to significant difficulties in daily life, and disrupt educational and occupational progress.

Although consensus clinical guidelines for physical aspects of TSC were established at a NIH TSC conference in Annapolis, USA, in 1998, no specific guidelines were given on which behavioural and cognitive aspects to assess in TSC. To redress this situation, a consensus workshop was convened in 2003 in Cambridge (UK) with the financial support and endorsement of the Tuberous Sclerosis Association (UK) and the TSAAlliance (USA). The aim was to produce clinical guidelines for cognitive and behavioural assessments of individuals with TSC using up to date evidence from research studies. The panel included parents of individuals with TSC, psychiatrists, neuropsychologists, psychologists, paediatric neurologists, and special needs teachers. The research evidence as it is presently available and the consensus clinical guidelines were published in full in July 2005, in the journal, *European Child and Adolescent Psychiatry*: de Vries P, Humphrey A, McCartney D, Prather P, Bolton P, Hunt A. *Consensus clinical guidelines for the assessment of cognitive and behavioural problems in Tuberous Sclerosis*, *European Child and Adolescent Psychiatry*. 2005 Jul;14(4):183-90. The information and Tables in this short summary are reproduced from the journal paper with the permission of the publishers.

Guidelines previously established for the assessment of the clinical manifestations of TSC included very little detailed advice on neurodevelopmental testing. However, the growing body of literature substantiates the very high prevalence of cognitive and behavioural problems in individuals with TSC that warrants as much emphasis on assessment and treatment as the physical problems. The guidelines presented here offer advice on the assessments that are recommended to be performed at various stages in a child or adult's life in two broad areas: firstly, cognitive assessments to enable maximum support to be given for future cognitive development; and secondly, behavioural assessments to diagnose problems that require psychiatric or psychological intervention. The *stages* when assessments are recommended are common to all children and adults with TSC. However, the *tests* administered, the subsequent educational programmes developed and any clinical treatment offered should remain tailored to the individual, their age and the local and national context.

The guidelines recommend areas that should be targeted in the context of TSC, but are not meant to imply limiting assessments only to those areas.

The guidelines presented here are a consensus of expert opinion based on the best available evidence in the field. All peer-reviewed publications relating to cognition and behaviour in TSC

were used in the preparation of these guidelines and references are given in the full paper (de Vries et al). Unlike other disabling conditions such as Down's syndrome or Fragile-X syndrome, many aspects of cognition and behaviour in TSC have received little systematic research so far and in particular areas such as language and academic skills lack full research. The guidelines are intended as advice to professionals who have individuals with TSC in their care, and as guidance to individuals, parents and caregivers about stages when assessments should be sought.

Summary of cognitive and behavioural difficulties in TSC

Tuberous sclerosis (TSC) is associated with a range of serious behavioural and cognitive difficulties in individuals with and without learning disability. Table 1 summarises these difficulties in TSC. The range of behavioural problems include sleep disturbance, aggressive behaviours, specific phobias, self-injury, temper tantrums, depressed mood and anxiety. In particular, there is strong evidence for high rates of ADHD, autism and ASD, and these can also occur at the same time as developmental disorders. Similar to the physical manifestations of TSC, there is great variability in the occurrence and severity of these problems between individuals, even in monozygotic twins. Developmental disorders, socially unaware and disruptive behaviours are most often seen in childhood and adolescence, whereas in adulthood high rates of anxiety symptoms and depressed mood are reported.

Table 1 Cognitive and behavioural problems associated with Tuberous Sclerosis

Cognition	Behaviour
Global cognitive deficits: mental retardation (WHO)/learning difficulties Specific cognitive deficits: <ul style="list-style-type: none"> • Social-communication deficits • Receptive and expressive language deficits • Attentional deficits (selective attention, sustained attention and attentional switching) • Executive deficits (planning, poor sequencing, perseveration) • Memory deficits (working memory, episodic memory) Motor deficits <ul style="list-style-type: none"> • Motor abnormalities (fine motor, gross motor, movement disorders) 	Autism, Asperger's and other autism spectrum disorders (ASD) ADHD and related disorders Aggression, rage outbursts and temper tantrums Negativity (temporary resistance to change) Emotional lability Depressive disorders Anxiety disorders Sleep disorders Epilepsy-related psychotic disorders

Intellectual abilities in TSC divide individuals approximately into two groups. Around 55% function within the normal range of IQ (>80) while the rest have moderate to profound handicaps, with about 30% with global intellectual ability in the severe to profoundly impaired range (IQ<21) A study of early cognitive development in a clinic based sample of infants with TSC found that intellectual deficits are frequently apparent by one year of age and that these children did not show any evidence of 'catch-up' in development by 30 months of age.

In some children with TSC developmental outcome and progress may be correlated with the severity of seizure disorder and its control and those with intellectual impairments are more likely to have ASD, or disruptive behaviours but neither learning disability nor epilepsy are necessary or sufficient to explain the high rates of these behavioural disorders. There is also a high prevalence of significant language delay, even in those with normal intelligence.

Among children and adults with TSC who have normal intelligence, there is increasing evidence of specific cognitive deficits in attentional and executive skills, even in individuals without criteria for ADHD such as impulsivity or hyperactivity. People with problems in executive control processes may be inefficient and even inept in managing tasks that require planning, organisation, monitoring and judgement. Memory skills may also be impaired in normally intelligent adults with TSC, particularly in retrieval of encoded memories. All these problems could also occur in people with moderate to profound intellectual disability who cannot be evaluated on the tests available at present.

In the more able group, parents report significant difficulties in academic performance such as in reading, writing and arithmetic although these have not been researched in TSC. There were also reports that adults had difficulties in occupational functioning, such as in establishing a career or vocation, and in the ability to 'multi-task' in the workplace. These problems can lead to very high rates of low self-esteem, and the consequent high burden of care and stress on families. In some areas, difficulties are reported in obtaining appropriate services from statutory and non-statutory agencies such as educational authorities, social services departments, health care professionals or insurance companies due to the lack of understanding of the problems specific to TSC that have been identified by research.

Rationale for the Guidelines

Research has shown that TSC is a brain disorder with a high prevalence of cognitive and behavioural difficulties. Some of these difficulties, such as ASD or ADHD, will have clear social consequences and require intensive help and support. Others, such as attention or memory deficits could easily be missed in a normally intelligent child and quite severe educational problems can follow. It is therefore important to know if a child or adult with TSC has such difficulties or not. If a child is routinely checked for problems known to be associated with TSC, backed up by accepted assessment tests, this would then enable a child to be offered, from the beginning, an individual remedial programme if it is required. It can never be good practice to put such a child or adult, without assessment, into a situation where they fail and only *after* failure assess them and offer help. Routine checks would minimize the risk of added complications developing, thus avoiding not only expensive and protracted interventions but also the emotional trauma induced in a child or adult who fails.

Panel recommendation I: Perform regular assessment of cognitive development and behaviour to identify and treat emerging difficulties and to establish a baseline for evaluating any later changes.

Assessments should be tailored to the presentation of problems shown by each individual and performed at the recommended ages, as shown in Table 2. The pre-school assessments should be routinely done to identify developmental and behavioural impairments that otherwise can be difficult to identify in young children and to establish a baseline measure against which any future changes may be compared. *Extra assessments may be necessary if new clinical concerns emerge as the child develops.* Evaluations should use neuropsychological and behavioural tools appropriate to the developmental level of the individual so that these results can be interpreted against those of the population at large.

It may not be necessary or appropriate to assess for every area of difficulty in every individual at every age. Global cognitive, motor and language development will be very important in infants and young children, but emotional problems and skills needed for independent living will be more relevant to adolescents and adults. Assessment of the various areas will involve different

professionals such as developmental or community paediatricians, speech and language therapists, clinical or educational psychologists and psychiatrists in child and adolescent, adult and learning disability services. These cognitive and behavioural profiles will be useful to the local multidisciplinary care team, in planning the services needed by the person with TSC and will enable a review of longitudinal progress and response to treatment and support.

Panel recommendation II: Perform a comprehensive assessment when there are changes in cognitive development or behaviour to identify and treat the underlying causes of neurobehavioural change

Changes in behaviour (e.g. increased aggression, withdrawal or change in sleep patterns), regression in development (e.g. loss of language or motor skills), deterioration of academic or vocational abilities or changes in physical manifestations (e.g. change in seizures, vision) should always be assessed and appropriately investigated. Regression and deterioration of functional abilities are not characteristics of TSC, but may result from a range of biological, psychological and social factors such as seizures, pain, renal failure, medications, onset of a psychiatric illness or changes in the routine or environment of an individual with severe learning difficulties. In a small but significant minority of individuals, subependymal giant cell astrocytomas (SEGAS) may develop and produce complications either through invasion of surrounding cerebral tissue or through blockage of the flow of cerebrospinal fluid through the foramen of Munro and the precipitation of pressure hydrocephalus. In such circumstances there may be an associated deterioration in behaviour and intellectual ability or potentially the emergence of specific cognitive impairments.

It is recommended that investigations of these changes include a comprehensive physical and neurological review, functional analysis of behaviour, neuropsychological evaluation and appropriate special investigations such as biochemical profile, EEG and MRI.

Consensus Panel Guidelines

The consensus guidelines for routine cognitive and behavioural assessments are presented in Table 2 and recommend assessments at set stages. For each assessment stage, the age range for the assessment is given and the general purpose of assessment are outlined. Specific concerns to pay attention to in TSC are also listed for each stage. Even if an early assessment is within normal limits, re-assessment should be performed when the individual is moving into a new educational or social environment. Any subtle deficits identified should be recorded and taken into account by educators, families and other relevant professionals should problems arise.

Table 2 Consensus guidelines for cognitive and behavioural assessments in Tuberous Sclerosis. The table shows the regular time points for assessment of all individuals with TSC.

Assessment stage	Age range for assessment	General purpose of assessment	General areas to assess	*Areas of particular concern in TSC:	*Behavioural and learning problems of particular concern in TSC
At diagnosis		Initial assessment of cognitive and behavioural profile	As listed for chronological age		
Infancy	0– 12 months	To perform a baseline assessment for regular monitoring of development	Global standardised assessment of infant development	Impact of seizure onset and treatment on development	
Toddler	1y – 2y11m	To identify early developmental delay or	Global cognitive ability and		Autism and Autism

		developmental disorders	adaptive behaviours Specific skills: Gross and fine motor skills Social-communication skills	Quality of eye-contact, joint attention, reciprocity	Spectrum Disorders (ASD) Severe aggressive outbursts Severe Sleep Problems
Pre-school	3y to school entry	Evaluation of cognitive and behavioural profile to ensure the provision of appropriate educational programmes	Global cognitive ability Specific cognitive skills: Receptive and expressive language Social communication skills Attentional-executive skills Visuospatial skills Motor skills	Uneven profile of abilities Poor expressive language Poor reciprocity, peer interaction Poor regulation of affect and impulse Poor bilateral co-ordination	Autism and ASD ADHD and related disorders Self-injurious behaviour
Early school years	6y – 8y	Monitoring the child's ability to make appropriate educational progress	Global cognitive abilities Specific cognitive skills: Receptive and expressive language Social communication skills Memory Attentional-executive skills Visuospatial skills Motor skills	Best time to establish baseline to assess whether specific cognitive skills and scholastic performance is discrepant from global intellectual abilities Poor expressive language and word retrieval Rote learning difficulties Selective attention, sustained attention difficulties	Specific scholastic difficulties (reading, writing, spelling, mathematics) ADHD and related disorders Peer problems Aggressive behaviours
Middle school years	9y – 12y	Complete review of child's abilities, specific learning difficulties and behavioural problems in preparation for the transition to secondary education	Global cognitive abilities Specific cognitive skills : Receptive and expressive language Social communication skills Memory Attentional-executive skills	Subtle deficits of social-communication, unusual interests Poor short-term memory, episodic memory Planning, organisational abilities, multi-tasking difficulties	Asperger's Syndrome Peer problems Scholastic difficulties (reading, writing, spelling, mathematics)
Adolescence	13y – 16y	Determining individual needs	Global cognitive abilities		Depressive disorders

		and the support required for transition into adult life	Specific cognitive skills Attentional-executive skills Vocational assessment with knowledge of cognitive strengths and weaknesses Adaptive behaviour and daily living skills	Poor judgement, decisionmaking	Anxiety disorders Peer problems
Adults	18y+	<u>Newly diagnosed adults:</u> assessment of cognitive, behavioural and vocational profile, determining bio-psycho-social needs	Global cognitive abilities Specific cognitive skills: Attentional-executive skills Memory	Difficulty with integrational skills Working memory, episodic memory problems	Depressive disorders Anxiety disorders Epilepsy-related psychotic disorders
Adults (follow-up)	18y+	Monitoring for emergence of psychiatric problems or changes in existing cognitive and behavioural difficulties	<u>Dependent adults:</u> Annual review of social care needs and support <u>Independent adults:</u> Vocational advice Genetic counselling as appropriate Review if problems arise	Pay particular attention to <i>change</i> in cognitive abilities or behaviour Pay particular attention to <i>change</i> in cognitive abilities, vocational performance and behaviour	Depressive disorders Anxiety disorders Epilepsy-related psychotic disorders

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

* Many features listed in these columns can present at any age, but are listed here at stages most commonly associated with the emergence of such difficulties in TSC

Neuropsychological tests

There is a wide range of neuropsychological tests in general use in different countries, with some that are routine in pre-school or school settings, and others that are more specialized tools derived from research studies. Some of the tests most often used in the UK are shown in Table 3 but those used will depend on local resources and preferences. However the areas of potential difficulty will not vary and it is important that these are assessed appropriately.

Table 3 -Tests for Clinical Assessment of Cognition and Behaviour

The following tests should be readily available in the UK for use by appropriately qualified clinical or educational psychologists. Approximate ages of suitability are given in brackets.

AGE 0-4 years, Infants and pre-school

Development

Readily available

Bayley Scales of Infant Development –2nd Edition
Griffiths (general development)

Age range of test

1-42 months

0-8 years

0-12 years

Vineland Adaptive Behavior Scales (communication and social skills)

2 yrs 6m -7 yrs 3m

3-12 years

Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)
NEPSY (to assess general neuropsychological development)

2 yrs 11m to 20 years

0-3 years

2-18 years

Leiter, Snijders-Oomen (non-verbal intellect)

Sometimes available

Mullens Scales of Early Learning

Beery VMI (visual and motor skills)

15m to 7 yrs 6m

3-7 years

Pre-school - language development

Reynell Developmental Language Scales III

Preschool Clinical Evaluation of Language Fundamentals (CELF-
Preschool)

1yr 6m – 3 years

Pre-school - behaviour

CHAT (Autism- first general screening)

AGE 5-17 years

Children – Global cognition/intelligence

Wechsler Intelligence Scale for Children – 4th edition (WISC-III/IV)
Ravens Progressive Matrices

6 yrs – 16 yrs 11m

5-11 years

Children – Visuospatial and motor skills

Readily available

Kaufman KABC-II

3-18 years

Sometimes available

Wide Range Assessment of Visual Motor Abilities (WRAVMA)

3-17 years

Children –Language

Clinical Evaluation of Language Fundamentals (CELF-3)

6-16 years

Children – Memory

Readily available

Children's Memory Scale

5-16 years

Doors and People

5-11years

5-90 years

Wide Range Assessment of Memory and Learning-2 (WRAML-2)

8years -Adult

Sometimes available

Benton Visual Retention Test

6-16 years

3-12 years

Children – Attention and concentration

Test of Everyday Attention for Children (TEACh)

NEPSY

6 yrs – 16 yrs 11m

Children –Formal scholastic skills	<i>6-16 years</i>
Wechsler Objective Language Dimensions (WOLD)	<i>6yrs - 16 yrs6m</i>
Wechsler Objective Reading Dimensions (WORD)	<i>4yrs -16yrs6m</i>
Wechsler Objective Numerical Dimensions(WOND)	<i>7-15 years</i>
Wechsler Individual Achievement Test (WIAT-II)	<i>3-12 years</i>
Children – Higher 'executive' function/'logic'	<i>2years +</i>
Tower of London	
NEPSY	<i>2years –Adult</i>
	<i>Single words – fluent adult</i>
Autism and ASD	
<u>Readily available</u>	
Childhood Autism Rating Scale (CARS)	
<u>Sometimes available</u>	<i>6 years +</i>
Autism Diagnostic Interview- Revised , ADI-R	<i>3-16 years</i>
	<i>6-18 years</i>
Autism Diagnostic Observation Schedule ADOS	
Behavioural difficulties (for the carer to complete regarding the child)	
<u>Sometimes available</u>	
Social Communication Questionnaire (SCQ)	
Strengths and Difficulties Questionnaire	
K-SADS Psychopathology	
<u>ADULTS 18+ years</u>	
Adults – Global cognition/intelligence	
Wechsler Adult Intelligence Scale- Third Edition (WAIS-III)	<i>16-89 years</i>
Ravens Progressive Matrices	<i>6yr-Adult</i>
Adults – Visual, spatial and motor skills	
<u>Readily available</u>	<i>18+</i>
Visual Object and Space Perception battery (VOSP)	
<u>Sometimes available</u>	<i>6-89 years</i>
Grooved Pegboard tasks	<i>8yr –Adult</i>
	<i>Child to Adult</i>
Benton Visual Retention Test (BVRT)	
Rey Complex Figure Test copying	<i>18-80 years</i>
	<i>16-96 years</i>
Adults – Memory	
<u>Readily available</u>	
Doors and People	<i>16 – 89 years</i>
Rivermead Behavioural Memory Test (RBMT-II)	<i>Child – Adult</i>
<u>Sometimes available</u>	
Wechsler Memory Scale-Third Edition (WMS-III)	<i>18-80 years</i>
	<i>19-83years</i>
Rey Complex Figure Test recall	

Adults – Attention and concentration	
Test of Everyday Attention, TEA	<i>18-80 years</i> <i>16-87 years</i>
Behavioural Inattention Test BIT –unilateral neglect	<i>Adult</i> <i>6yrs5m – 89 years</i> <i>8-89 years</i>
Adults – Higher 'executive' function	
<u>Sometimes available</u>	
Hayling and Brixton tests	
Behavioural Assessment of the Dysexecutive Syndrome (BADS)	<i>Adult</i> <i>13-80 years</i>
Verbal fluency (COWAT)	
Wisconsin Card Sorting test (WCST)	
Trail making tests	
Adults –Behaviour	
SADS/M-SADS Psychopathology	
Beck –Depression, anxiety	

The clinical diagnosis of psychiatric disorders should be made according to established international diagnostic criteria such as ICD-10 and DSM-IV. A range of supplemental tools such as interviewer-based schedules, observational schedules and behavioural rating scales are available to aid the diagnostic process by clinicians.

Post-assessment interventions

These clinical guidelines do not present information on specific post-assessment interventions but if specific difficulties are identified at any of the assessment stages, the child or adult should be managed or referred as clinically appropriate. Management strategies are likely to involve a range of clinical specialities and multi-agency involvement. Table 4 lists a range of possible outcomes of neurobehavioural assessments.

Table 4 Possible outcomes of neurobehavioural assessment of individuals with tuberous sclerosis.

<ol style="list-style-type: none"> 1. Arrange further detailed evaluations (including functional analysis of behaviour, physical review and special investigations) 2. Enrol child in community programme for early intervention 3. Develop specific therapeutic programme for a child's developmental needs (pre-school, primary school, secondary school and post-school) 4. Statutory assessment of special educational needs before the child begins formal education 5. Perform an annual review of progress and educational needs 6. Refer to social services departments and other agencies for respite and/or daily living support 7. Liaison with children's disability teams 8. Refer for or provide appropriate psychological support and psychiatric intervention including psychopharmacology 9. Assess support required for vocational training and daily living in adult life

TSC Behaviour Consensus Panel Members

These consensus guidelines were compiled at the TSC Brain/Behaviour Workshop held January 10-12th 2003 in Cambridge, UK and financially supported by the Tuberous Sclerosis Association (UK) and the Tuberous Sclerosis Alliance (USA)

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From www.tuberous-sclerosis.org