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## A clinical update on Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND)

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### Abstract

Tuberous Sclerosis Complex (TSC) is associated with a wide range of behavioural, psychiatric, intellectual, academic, neuropsychological and psychosocial difficulties that are often under-diagnosed and under-treated. Here we present a clinical update on TSC-associated neuropsychiatric disorders, abbreviated as “TAND”, to guide screening, diagnosis and treatment in practice. The review is aimed at clinical geneticists, genetic counsellors, paediatricians and all generalists involved in the assessment and treatment of children, adolescents and adults with TSC and related disorders. The review starts with a summary of the construct and levels of TAND, before presenting up-to-date information about each level of investigation. The review concludes with a synopsis of current and future TAND research.

### Keywords

TSC; TAND; behaviour; mental health; autism spectrum disorder; ADHD; anxiety; depression; scholastic difficulties; neuropsychological deficits

## 1. INTRODUCTION

Tuberous Sclerosis Complex (TSC) is a multi-system genetic disorder associated with a wide range of physical manifestations, including in the brain, skin, kidney, eye and lung (Curatolo, Moavero, & de Vries, 2015; Henske et al., 2016). These manifestations have an

age-related expression, and therefore become manifest at different timepoints in the lifespan of an individual with TSC (Curatolo, Bombardieri, & Jozwiak, 2008). The brain, skin and kidney represent the most commonly affected organ systems in 80–90% of those with TSC.

Apart from the physical manifestations, most individuals with TSC are affected by a range of neuropsychiatric manifestations, seen in ~90% of individuals with TSC (Curatolo, Moavero, & de Vries, 2015; de Vries et al., 2015). These manifestations also have an age-related presentation, with different features typically emerging at different developmental timepoints (de Vries et al., 2005; de Vries, 2010a; de Vries et al., 2015). The neurological and neuropsychiatric features of TSC lead to the greatest burden of disease (Curatolo, Moavero, & de Vries, 2015; Hallett, Foster, Liu, Blieden, & Valentim, 2011; Rentz et al., 2015). Whilst there has been great progress in the identification and treatment of many of the physical features of TSC, including SEGA, angiomyolipoma and epilepsy, the neuropsychiatric manifestations remain highly under-identified and under-treated (Kingswood et al., 2017).

Here we present a clinical update on TSC-associated neuropsychiatric disorders, abbreviated as “TAND”, to guide screening, diagnosis and treatment in practice. The review is aimed at clinical geneticists, genetic counsellors, paediatricians and all generalists involved in the assessment and treatment of children, adolescents and adults with TSC and related disorders. We will start with a summary of the construct and levels of TAND, before presenting up-to-date information about each level of investigation. We will conclude with a synopsis of current and future TAND research.

## 2. THE CONSTRUCT AND LEVELS OF TAND

At the 2012 International TSC Consensus Conference set up to revise diagnostic criteria (Northrup et al., 2013) as well as surveillance and management guidelines for TSC (Krueger et al., 2013), the Neuropsychiatry Panel coined the term “TAND” (TSC-associated neuropsychiatric disorders) as an umbrella term to include the full range of neurodevelopmental, behavioural, psychiatric and psychosocial difficulties seen in association with TSC (de Vries et al., 2015; Krueger et al., 2013). The panel observed that the complexities of TSC requires multi-professional (e.g. multiple health professionals such as psychiatry, psychology, occupational therapy and speech & language pathology) and trans-disciplinary (e.g. from health, education and social care systems involving physicians, educators, social workers) input, as well as collaboration with a range of other statutory and non-statutory organisations. Across all these professions and sectors, different ‘language’ has been used to refer to various aspects of development, mental health or psychosocial needs. In order to generate a ‘shared language’ that might aid inter-professional communication and to guide future research, the panel defined 6 ‘levels of investigation’ and encouraged all professionals involved in the care of those with TSC to use this ‘shared language’. The levels of investigation and short definitions of each are presented in Table 1.

Given that TAND manifestations also have an age-related expression in a manner similar to the physical features of TSC, the International Consensus Panel recommended that all individuals with TSC should be screened for TAND at least once per year (Krueger et al.,

2013). The Neuropsychiatry Panel defined ‘screening’ in the context of TAND as a topline examination for any obvious or emerging TAND difficulties that may require comprehensive work-up or treatment. In order to support annual screening, the TAND Checklist was developed (de Vries et al., 2015) and pilot validated (Leclezio, Jansen, Whittemore, & de Vries, 2015). The TAND Checklist is a pen-and-paper tool to help guide a conversation between the clinician and the family (or person with TSC wherever they are able to participate directly). It is suitable for individuals of all ages and abilities, and consists mainly of a series of YES/NO items across the levels of investigation outlined in this review. For further details of the TAND Checklist, please see (de Vries et al., 2015) where a free downloadable copy of the TAND Checklist is available. Over the last few years, a number of translations of the TAND Checklist have been made in partnership with TSC user/carer organisations and key clinicians in different countries. Language versions to date include Spanish, German, Swedish, Dutch, Italian, Polish and Catalan. Further details about translations are available from the authors.

Below we will summarise current evidence for each of the TAND levels of investigation, including basic guidelines for further evaluation and intervention.

### 3. THE BEHAVIOURAL LEVEL

The behavioural level of TAND consists of behaviours that are not in and of themselves psychiatric disorders, but which can cause concern for individuals with TSC, their families or professionals. As such they are often the reason why individuals with TSC are referred onwards for psychological or psychiatric assessment. The largest dataset including behavioural features of TAND to date, the TuberOus SClerosis registry to increase disease Awareness (TOSCA), indicated that 36% of individuals with TSC reported at least one behavioural problem, with overactivity, impulsivity and sleep difficulties being the most common behavioural problems, affecting around 20% of individuals (Kingswood et al., 2017). Anxiety, mood swings and severe aggression were also relatively common, affecting 11–14% of individuals, and depressed mood, self-injury and obsessional behaviours were reported in 6–8% of individuals (Kingswood et al., 2017). Estimated rates of TAND behavioural difficulties from other studies have typically been higher than those reported from the TOSCA registry, which has substantial diversity in intellectual ability and age. This diversity may reflect the TSC population. However, it is also known that both age and intellectual ability influence the manifestation of TAND behaviours, with more difficulties generally reported in individuals with intellectual disability (ID) and in children (de Vries, Hunt, & Bolton, 2007; Wilde et al., 2017). Given the significant proportion of unreported or missing data identified in the TOSCA study, the study authors proposed that the low reported rates identified in TOSCA suggested that, even in TOSCA participating centres, TAND manifestations were typically under-identified and under-treated (Kingswood et al., 2017). Table 2 (updated and expanded from Leclezio & de Vries, 2016) illustrates the variability in estimates of rates of TAND behaviours and the influence of ability and age.

Reported rates of anxiety in TSC are higher than those of low mood, both in adult and child samples as shown in Table 2 and in de Vries, Hunt & Bolton, 2007. In contrast to most behavioural problems in TSC, those relating to low mood and anxiety do not seem to be

different between those with and without ID (de Vries, Hunt, & Bolton, 2007). All carers and professionals should therefore be vigilant for such difficulties and implement proactive management strategies where they are identified. In less able individuals (a significant proportion of the TSC population), communication difficulties may preclude self-report and behavioural symptomatology relating to mood may be underestimated. It is important therefore that appropriate tools, such as the TAND Checklist (de Vries et al., 2015) are used to evaluate and monitor these behavioural features of TAND.

Upper estimates, all from children and adolescents with ID (see Table 2), indicate that over two-thirds of this age group show self-injury, aggressive outbursts and/or temper tantrums. Rates of self-injury are significantly lower in children and adolescents without ID (de Vries, Hunt, & Bolton, 2007), and also in adults who have ID (Wilde et al., 2017), suggesting that this behaviour is sensitive to gains in both age and ability. Children with severe ID are therefore a particularly high-risk group for this deleterious behavioural outcome. Aggressive outbursts and temper tantrums in children and adolescents with TSC have been reported to be much more stable across ability levels (de Vries, Hunt, & Bolton, 2007), although aggressive outbursts also seems to reduce into adulthood. Aggression in adults with TSC who have ID is reported at lower rates than children and adolescents without ID and mixed ID/no ID samples (de Vries, Hunt, & Bolton, 2007; Eden, de Vries, Moss, Richards, & Oliver, 2014). This suggests that childhood might be a high-risk time for aggressive behaviour for all children with TSC, but, like self-injury, this may ameliorate with age.

Given the strong association between autism spectrum disorder (ASD) and TSC it is unsurprising that a range of social communication difficulties are described, although the TSC literature has focused more on psychiatric diagnostic status rather than on behavioural manifestations associated with ASD. Consistent with the relationship between ability and formal ASD diagnoses in TSC (Bolton, Park, Higgins, Griffiths, & Pickles, 2002; Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008), rates of behavioural difficulties in social communication in children and adolescents with TSC are associated with level of intellectual ability (see Table 2). However, even in those without ID, rates exceed those expected in the general population by at least 10-fold, thus evaluation and monitoring for these difficulties should be carried out across all levels of ability. In terms of the phenomenology of these behaviours, both children above and below diagnostic thresholds for ASD are reported to have specific deficits in imaginative play skills (Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008). For children who exceed ASD thresholds, toddlers with TSC and ASD are reported to demonstrate social communication behaviours that show 'remarkable convergence' with idiopathic ASD (Jeste et al., 2016). This contrasts with other syndromes where it has been suggested that individuals may exceed thresholds but have a different underlying profile of social communication behaviours (Moss, Oliver, Nelson, Richards, & Hall, 2013). The similarity between the profile of social communication difficulties in TSC and idiopathic ASD, supports the use of existing ASD interventions for individuals with TSC.

Examination of overactivity and impulsivity has also primarily considered psychiatric diagnostic status of Attention Deficit Hyperactivity Disorder, (ADHD) rather than behavioural presentation, with few studies even differentiating ADHD subtypes (Chung et

al., 2011; Huang, Peng, Weng, Su, & Lee, 2015). Evidence suggests that in children and adolescents, overactivity and impulsivity correlates strongly with the presence or absence of ID (de Vries, Hunt, & Bolton, 2007), and there is some indication that overactivity may decrease with age (see Table 2). More nuanced studies of overactivity and impulsivity are warranted to identify priorities for intervention for these problematic behaviours in TSC, particularly given robust associations between impulsivity and self-injury and aggression in TSC (Eden et al., 2014; Wilde et al., 2017; Wilde et al., 2018), suggesting that impulsivity may be a risk marker for these adverse behavioural outcomes.

Reports of sleep difficulties in TSC vary widely and likely depend heavily on the measures used. The lower estimates in Table 2 are of specific topographies of sleep disorder (settling and early morning waking; rates of night waking were much higher at 45%), the higher rate is from a study that asked a broader question about sleep problems in general. Carer reports of night waking problems (Hunt & Stores, 1994; Trickett, Heald, Oliver, & Richards, 2018) are supported by direct polysomnography assessment in children with TSC, which found shorter total sleep duration (Bruni, Cortesi, Giannotti, & Curatolo, 1995). Other sleep behaviour problems include daytime sleepiness, parasomnias, and increased rates of co-sleeping (Trickett et al., 2018). Associations between health problems (which are common in TSC) and poorer sleep suggests that intervention for health problems may improve sleep. Further, an association between sleep difficulties and daytime overactivity/impulsivity may suggest that intervening for poor sleep could improve other behavioural difficulties in TSC (Trickett et al., 2018).

The diversity of the behavioural manifestations of TSC and the variable influence of age and ability and interactions between behaviours pose a challenge for evaluating this level of TAND. Each individual with TSC may have a unique TAND 'signature' (Leclezio, Gardner-Lubbe, & de Vries, 2018) and this complexity may overwhelm families and lead to treatment paralysis for professionals (Leclezio & de Vries, 2015). Identifying clusters of TAND behaviours may help to reduce this complexity. While there are 'top-down' groupings of these TAND behaviours (e.g. relating to psychiatric diagnostic categories) there has never been an exploration of the natural grouping of the behavioural manifestations of TSC until recently. A feasibility study of identifying natural TAND clusters found 6 clusters, of which 4 included the majority of behavioural variables (Leclezio, Gardner-Lubbe, & de Vries, 2018). These were 'ASD-like' (delayed language, repetitive behaviour, difficulties with eating, and self-injury), 'behavioural dysregulation' (temper tantrums, mood swings, aggressive outbursts), 'hyperactive/impulsive' (overactivity, restlessness and impulsivity) and 'mood/anxiety' (anxiety, depressed mood, sleep difficulties). This suggests potential for a more streamlined approach to understanding and evaluating TAND behaviours for both families and professionals, which may in turn reduce treatment paralysis in TSC and improve outcomes for those experiencing behavioural difficulties.

#### 4. THE PSYCHIATRIC LEVEL

The psychiatric level of TAND includes different manifestations across the lifespan of individuals with TSC, with ASD and ADHD typically seen in infancy and childhood, and anxiety and depressive disorders in adolescence and adulthood.

#### 4.1 Neurodevelopmental Disorders

**Autism Spectrum Disorder (ASD)**—TSC represents one of the major single gene disorders causing ASD (Curatolo, Moavero, & de Vries, 2015; de Vries, 2010a). The prevalence of ASD in TSC is widely variable according to the different studies, but averages between 40 and 50% (Curatolo, Moavero, & de Vries, 2015). Potential factors increasing the risk for ASD include TSC gene mutation, structural brain abnormalities and epilepsy. Although a prediction of the behavioural phenotype is not yet possible, ASD is clearly more commonly seen in individuals with *TSC2* mutations. Mutations occurring in the hamartin interaction domain of *TSC2* have been reported to have a relation with ASD (Numis et al., 2011), but this finding has not been replicated. Regarding brain abnormalities, tuber-brain proportion, cystic tubers and white matter abnormalities have been identified as possible risk markers for ASD (Numis et al., 2011). However, given the clearly complex and multi-componential pathophysiology of ASD, it is also important to be mindful that neither mutation status, structural abnormalities or seizures are necessary or sufficient to predict ASD in TSC (Curatolo et al., 2010; de Vries & Howe, 2007; Schneider, de Vries, Schonig, Rossner, & Waltereit, 2017; Waltereit, Japs, Schneider, de Vries, & Bartsch, 2011).

As a consequence of mutation in one of the two TSC genes, the fetal activation of mTOR pathway confers a higher risk both for epilepsy and ASD, via alteration of synaptogenesis, long-term potentiation, alteration of GABA/glutamate balance, and a range of putative intracellular aberrations (Curatolo et al., 2016; de Vries & Howe, 2007; Prabowo et al., 2013). However, infants with earlier age of seizure onset, higher seizure frequency, and more EEG abnormalities proposed to be particularly in the temporal lobes, are at higher risk for ASD, with all these factors acting as adjunctive risk factors (Bolton et al., 2002; Numis et al., 2011). Recent evidence also showed that in subjects with early onset and refractory seizures, there is a significant alteration of white matter connectivity in areas playing a role in ASD, such as the cingulate cortex (Moavero et al., 2016). This makes early and prompt antiepilepsy treatment necessary to minimize the long-term sequelae of early-onset seizures. In fact a longer gap between seizure onset and treatment initiation has been shown to be associated with a higher rate of ASD when compared to a prompt treatment in the first week from seizure onset (Cusmai, Moavero, Bombardieri, Vigevano, & Curatolo, 2011). Whether antiepilepsy treatment in TSC should be started before the onset of seizures is still a matter of debate, and a prospective multi-centre study is now ongoing trying to answer this question such as the EPISTOP ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and PREVENT trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT02098759 & NCT02849457).

Early autistic traits can be identified in subjects with TSC already in the first year of life, with alterations of playing, social interaction and eye gaze (Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008). After the second year of life, abnormal behaviours including hyperactivity, rituals, repetitive behaviours, and temper tantrums can appear (Jeste, Sahin, Bolton, Ploubidis, & Humphrey, 2008). A slowing of development in verbal skills in the first years of life could predict the subsequent diagnosis of ASD (Jeste et al., 2014). Children with TSC and ASD usually show lower intellectual abilities when compared to children with TSC without ASD, and this difference is already evident at 12 months of age (Jeste et al.,



2014). From a phenomenological point of view, children with ASD associated with TSC do not seem to differ from children with idiopathic ASD (de Vries, 2010a; Jeste et al., 2016).

An early recognition of symptoms of ASD is of crucial importance to start prompt and appropriate evidence-based interventions for ASD. Very little direct evidence has been established in TSC, apart from a small pilot of JASPER ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT03422367). However, clinicians are advised to seek comprehensive assessments and interventions for ASD in infants and children with ASD in the same way as they would for children without TSC.

In spite of the theoretical value of mTOR inhibitors as treatment for ASD, most evidence to date is based on animal models (Schneider, de Vries, Schonig, Rossner, & Waltereit, 2017; Tsai et al., 2012; Waltereit, Japs, Schneider, de Vries, & Bartsch, 2011) or preliminary evidence in humans of a possible good response (Kilincaslan et al., 2017). A number of early-phase clinical trials are examining this question ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), but no clinical recommendations about mTOR inhibitors for ASD in TSC can be made to date.

**Attention Deficit Hyperactivity Disorder (ADHD)**—ADHD occurs in about 30–50% of subjects with TSC (de Vries, Hunt, & Bolton, 2007; Gillberg, Gillberg, & Ahlsen, 1994; Hunt, 1993; Muzykewicz, Newberry, Danforth, Halpern, & Thiele, 2007) thus being ten times more prevalent than in the general population (de Vries, 2010a). The pathogenesis of ADHD in TSC is still largely unknown, but several factors have been suggested to contribute to the risk of ADHD, such as frontal lobe epilepsy and/or EEG abnormalities, especially in the presence of structural frontal lobe abnormalities, and the presence of a *TSC2* mutation (D'Agati, Moavero, Cerminara, & Curatolo, 2009; Muzykewicz et al., 2007). A susceptibility locus for ADHD has been identified on chromosome 16p13, where the *TSC2* gene is located, encoding for the NMDA receptor 2A, and abnormal glutamatergic transmission can play a crucial role in the pathogenesis of ADHD (Carrey, MacMaster, Gaudet, & Schmidt, 2007; Ogdie et al., 2004; Turic et al., 2004). However, we acknowledge that, as is the case for ASD, it is not yet clear whether the ADHD risk associated with *TSC2* mutations is mediated through the risk for intellectual disability (ID) or occurs independent of ID.

Apart from a clinical diagnosis of ADHD, subjects with TSC can show lower attentional abilities across a number of attentional components, but no specific patterns of neuropsychological attention deficits has been identified to date. These will be discussed in further detail under the neuropsychological level.

There have been no treatment studies of ADHD in TSC to date. Clinicians are therefore advised to use evidence-based treatments and practice parameters for ADHD in individuals without TSC (Pliszka et al., 2007). Apart from the theoretical risk that stimulant medications (such as methylphenidate) may reduce seizure threshold, there is no evidence in TSC to support this. Clinicians are therefore advised to use stimulant medications if clinically indicated, following the same guidelines, mindful and cautious of any potential physical risks.

## 4.2 Anxiety and Depressive Disorders

In spite of the high rates of anxiety and depressive symptoms as outlined under the behavioural level, there have been relatively few studies of anxiety and depressive disorders in TSC. Lewis and colleagues (Lewis, Thomas, Murphy, & Sampson, 2004) highlighted the high rates of anxiety symptoms in intellectually able adults with TSC (56%) and pointed out that none of them had received any comprehensive evaluation or treatment for their anxiety disorder. She proceeded to perform systematic evaluations and confirmed a high rate of anxiety disorder meeting ICD-10 criteria. A retrospective study on a clinic series of individuals with TSC identified anxiety disorder in 28% and depressive disorder in 27% of individuals evaluated by a psychiatrist (Muzykewicz et al., 2007). Lewis did not find an association between *TSC1* vs *TSC2* in relation to anxiety or depressive disorder, however, the Muzykewicz data found a significant correlation with *TSC2* status. This question therefore clearly still requires further examination before any firm conclusions can be drawn.

The TOSCA (TuberOus SCLerosis registry to increase disease Awareness) registry identified anxiety and depressive disorders in 9.1% and 6.1% respectively where data were available (Kingswood et al., 2017). The mean ages at diagnosis were 17.8 years for anxiety and 24.4 years for depression, thus underlining the typical age of onset in adolescence and adulthood. Importantly though, TOSCA did identify infants and children with anxiety disorders, emphasising the need for comprehensive evaluations at all key developmental timepoints (de Vries et al., 2005). The TOSCA study collected data on genotype and intellectual ability, and may therefore be able to answer the question regarding the association between *TSC1* vs *TSC2* status in relation to anxiety and depressive disorders, once controlled for intellectual ability.

In terms of treatment, there are very limited data available to guide TSC-specific treatment of anxiety and depressive disorders. Clinicians are therefore advised to use the standard evidence-based treatment approaches and practice parameters as outlined for anxiety and depressive disorders in individuals without TSC.

## 4.3 Other psychiatric disorders

Little systematic data have been collected on other psychiatric disorders seen in TSC (de Vries, 2010a). Psychotic disorders (including schizophrenia) have consistently been reported at low rates, very much in keeping with findings in the general population where the rate of schizophrenia is ~1%. In the TOSCA study, hallucinations (1.5%) and psychosis (2.3%) were reported at low rates (Kingswood et al., 2017). These findings are an interesting contrast to the very high rates of neurodevelopmental disorders in TSC. Obsessional behaviours, as discussed under the behavioural level, were observed in 6.1% of the TOSCA cohort. There have been no systematic studies of Obsessive Compulsive Disorder (OCD) in TSC to date. However, obsessional and repetitive behaviours are very common in association with ASD in TSC. Clinicians should therefore always consider a diagnostic work-up for ASD whenever they see children, adolescents or adults with TSC who present with obsessional characteristics.



## 5. THE INTELLECTUAL LEVEL

Individuals with TSC display a range of intellectual ability. Typically 40–50% have an IQ in the normal range of intellectual ability (Joinson et al., 2003; Kingswood et al., 2017). Although Joinson et al. (2003) noted that the mean IQ of individuals with TSC was within the normal range (IQ = 93.6), it was approximately 12 points lower than unaffected siblings without TSC (mean IQ = 105.6), representing a downward shift of the normal distribution. Some studies have noted higher rates (50–64%) of intellectual disability (IQ < 70) in individuals with TSC (Bolton et al., 2015; de Vries, Hunt, & Bolton, 2007; Gillberg, Gillberg, & Ahlsen, 1994; Goh, Kwiatkowski, Doren, & Thiele 2005; van Eeghen, Black, Pulsifer, Kwiatkowski, & Thiele 2012; van Eeghen, Chu-Shore, Pulsifer, Camposano, & Thiele, 2012), but these rates have been based on clinical or postal, rather than large-scale, population-based samples. Some investigations noted a bimodal distribution in IQ (de Vries & Prather, 2007; Jansen et al., 2008; Joinson et al., 2003), with one group of individuals on a normal distribution of IQ (referred to by de Vries & Prather as the ‘ND phenotype’), while another group fell in the profound or ‘P’ phenotype of intellectual ability. The bimodality has been linked to the presence of *TSC2* by some investigators (van Eeghen, Black et al., 2012). However, Wong and colleagues (2015) showed that *TSC1* and *TSC2* mutations had quite different patterns of distribution across intellectual or developmental quotients (IQ/DQ), and emphasized that genotype should not be used at an individual level to predict intellectual ability.

Interestingly, more recent studies have not replicated the bimodal distribution of IQ (Bolton et al., 2015; Kingswood et al., 2017). This may represent improved quality of care as suggested by some, or may be an artifact of measurement. From a clinical perspective the consistent observation in the TSC literature is that there is a considerable range of intellectual ability associated with TSC, from profound intellectual disability to very superior intellectual ability.

A number of factors have been explored as potential contributors or correlates to intellectual outcomes in TSC. Factors related to a higher risk for ID, including greater tuber load (Asato & Hardan, 2004), early onset of seizures, especially infantile spasms (Capal et al., 2017; Humphrey et al., 2014; Joinson et al., 2003; van Eeghen, Chu-Shore, et al., 2012), poor seizure control (Goh et al., 2005; van Eeghen, Chu-Shore, et al., 2012), and use of more antiepileptic medications likely reflecting more problematic seizure control (van Eeghen, Chu-Shore, et al., 2012), have all been examined. There may also be a dose-dependent effect of seizure activity on the development of ID. Humphrey et al. (2014) noted that in children with infantile seizures, IQ dropped from a mean of 92 before the onset of infantile spasms (IS), to a mean IQ of 73 after exposure to IS for less than one month, to mean of IQ = 62 after exposure to IS for more than one month. The presence of *TSC2* mutations have also been associated with a higher risk for intellectual disability (Dabora et al., 2001; Jansen et al., 2008; Jones et al., 1997; Kothare et al., 2014; Sancak et al., 2005), although considerable overlap in IQ distributions between *TSC1* and *TSC2* has been noted (Jansen et al., 2008; Wong et al., 2015).

In the most recent genotype-intellectual phenotype study, Wong and colleagues examined 100 individuals with known TSC mutations who were all assessed using a range of standardised intellectual/developmental level measures (Wong et al., 2015). Most individuals with *TSC1* mutations fell on a normal distribution of IQ with ~10% showing profound ID. Of those with *TSC2* mutations, 34% showed profound ID, and the rest fell on a ‘flattened’ and leftward shifted distribution of IQ quite different from *TSC1*. Interestingly, truncating *TSC1* mutations were all predicted to be subject to nonsense-mediated mRNA decay. Mutations predicted to result in unstable protein were associated with less severe effects on IQ/DQ, with a significant correlation between the length of predicted C-terminal tails and IQ/DQ. The authors proposed a model where IQ/DQ correlates inversely with predicted levels and/or deleterious biochemical effects of mutant TSC1 or TSC2. This hypothesis requires replication and biochemical testing (Wong et al., 2015).

Intellectual trajectories of TSC have also been studied. Van Eeghen and colleagues (van Eeghen, Chu-Shore, et al., 2012) studied intellectual ability in children and adults with TSC who had received repeated neurodevelopmental assessments (mean interval of 4 years). They noted that, although IQ remained essentially the same over time (mean decline = 2 points), there was considerable change in one-third of their sample, with 9/66 showing significant improvement and 11/66 showing significant deterioration. In contrast, there was a significant decline over time in adaptive behaviour, or practical living skills. This decline did not represent a regression (i.e., a loss of adaptive skills), but rather a failure to acquire new adaptive skills. Given that individuals with significant changes in intellectual outcomes were often younger and that variability over time stabilises as age advances, van Eeghen and colleagues proposed that infancy is a critical time when influences such as seizures can significantly alter brain development, supporting similar observations (Humphrey, Neville, Clarke & Bolton, 2006; Jeste et al., 2014).

IQ has been found to be similar in males and females with TSC (de Vries, Hunt, & Bolton, 2007; Joinson et al., 2003). Interestingly, van Eeghen, Black, et al., (2012) noted that, although IQ was similar in males and females with *TSC1* and *TSC2*, women with TSC who had NMI (no mutation identified) had a higher mean IQ (84) than men with NMI (mean IQ=77), although the clinical significance of a 7-point discrepancy and the range of scores were not discussed. Van Eeghen et al. (van Eeghen, Chu-Shore, et al., 2012) suggested that males with TSC were at higher risk for intellectual and adaptive declines over time, although this finding has not been replicated.

De Vries et al. (2007) and others noted that presence of ID has been associated with a higher risk for a range of behavioural manifestations (see also discussion under the ‘behavioural level’) including ASD-related (poor eye contact, repetitive behaviours) and ADHD-related (overactivity, restlessness, impulsivity), but not for mood and anxiety-related symptoms. They also noted a higher risk for self-injury in individuals with ID, as did Wilde et al. (2017), who also reported a higher risk for aggression in lower functioning individuals with TSC.

In summary, the intellectual level in TSC appears to be highly variable with about 50% of individuals in the ID range. The presence of ID represents a significant risk marker for other

TAND manifestations as outlined here, and for significant physical manifestations. Many individuals have very uneven profiles across verbal, perceptual, working memory and processing speed indices, even those with overall normal IQ, and it is therefore strongly advised that all individuals should have standardised evaluations of their intellectual ability to determine their overall intellectual profile and to identify specific areas of strengths and weaknesses.

## 6. THE ACADEMIC LEVEL

Even when overall intellectual ability is in the normal range, specific difficulties in academic or scholastic skills have been observed in TSC. Current DSM-5 terminology refers to these as 'specific learning disorders'. Jambaque et al. (1991) noted a high rate of dyscalculia (mathematics disorder), de Vries (2002) noted that 36% of school age children with TSC of normal intellectual ability were at high risk for academic disorders in reading, writing, and mathematics, and noted that mathematics disorders were especially common in children with TSC who also had ADHD (de Vries, 2010a). Carlisle (2004) reported that the majority of students with TSC are served in Special Education classrooms, with 75% of these children receiving services through the public school and 30% receiving private services. In addition to specific learning disorders, Prather and de Vries (2004) and de Vries (2010a) have noted that children with TSC are also at high risk for secondary deficits such as school refusal, anxiety about attending school, deficits in social skills, and low self-esteem.

Until recently, data on the academic level have been very limited. In the recent international TOSCA study of >2000 individuals with TSC (Kingswood et al., 2017), participants were asked how many ever had difficulties in academic performance and how many were ever assessed for academic difficulties. A total of 57.8% reported a lifetime history of academic difficulties. Strikingly, only 48.9% of those had ever received a formal assessment for these difficulties. Clearly much further research is required in this important level of TAND investigation.

Taken together, available results support the high rates of academic difficulties, but also underline the lack of evaluation and necessary support for these difficulties in the educational systems. For this reason, all individuals with TSC, including those with normal intellectual ability, should have regular evaluations for potential academic difficulties, and the majority are likely to benefit from an Individual Educational Plan (IEP/IEDP) to support their learning needs in school.

## 7. THE NEUROPSYCHOLOGICAL LEVEL

Individuals with TSC are at high risk for a range of neuropsychological deficits, even if they have normal IQ (Prather & de Vries, 2004). The most recent data from the TOSCA study identified 510 individuals (40.1% of the TOSCA cohort with available data) who had their neuropsychological skills assessed. Of those, 55% showed performance <5<sup>th</sup> percentile on formal measures, indicative of specific neuropsychological deficits (Kingswood et al., 2017).

## 7.1 Attentional deficits

De Vries and colleagues (de Vries, Gardiner, & Bolton, 2009; Tierney, McCartney, Serfontein, & de Vries, 2011) noted concerns in several aspects of attention, including selective attention, sustained attention, and attentional switching. A consistent deficit noted in both children and adults with TSC has been the ability to engage in dual-task performance, e.g., doing a visual search task while listening for an auditory cue (de Vries, 2002; de Vries, Gardiner, & Bolton, 2009; Tierney, McCartney, Serfontein, & de Vries, 2011). Although dual-task deficits have been proposed as a potential neuropsychological 'signature' of TSC (de Vries, 2002; Tierney, McCartney, Serfontein, & de Vries, 2011), it should be noted that there is considerable variability between individuals with TSC with respect to specific attention deficits (de Vries, Gardiner, & Bolton, 2009). Importantly, attention deficits have strong correlations with real-life difficulties, academic performance, and a sense of feeling overwhelmed (Tierney, McCartney, Serfontein, & de Vries, 2011). These neuropsychological deficits, however, do not necessarily correlate with behavioural attentional rating scales such as those used in ADHD (de Vries, Gardiner, & Bolton, 2009). For this reason, all individuals with TSC should be considered at high risk for neuropsychological attention deficits, not only those with behavioural manifestations of attentional problems. Concerns about attentional skills should lead to formal evaluation of this neuropsychological domain.

## 7.2 Memory deficits

In addition to attentional concerns, deficits in several aspects of memory have also been noted in individuals with TSC, even in individuals of normal intellectual ability (Davies et al., 2011; de Vries & Howe, 2007; Jambaque et al., 1991; Ridler et al., 2007). Ridler et al. (2007) noted deficits in recall memory (but not recognition), verbal memory, and spatial working memory in adults with TSC, relative to adults without TSC. A similar profile was observed by Davies et al. (2011) in a small study of adults. However, similar to the variability noted by de Vries et al. (2009) in attention, there was a significant variability between individuals with TSC on memory skills, with some participants being severely impaired (functioning < 5<sup>th</sup> percentile) in one or more areas, while others performed in the average to above-average range.

## 7.3 Executive deficits

Deficits in executive functioning, including planning, self-monitoring, cognitive flexibility, and goal-directed attentional behaviours have also been noted in adults with TSC (Curatolo, Moavero, & de Vries, 2015; Davies et al., 2011; de Vries, 2002; de Vries, 2010a; Harrison, O'Callaghan, Hancock, Osborne, & Bolton 1999). Prather and de Vries (2004) commented that overall, frontal systems appear to be the most consistently disrupted in TSC, leading to abnormalities in regulatory and goal-directed activities. Indeed, Tierney et al. (2011) reported that adults with TSC were rated as being significantly less functional on a behavioral questionnaire tapping attention-related behaviours in everyday activities. These sorts of deficits can have a devastating impact on an individual's ability to function in real-world living situations, including their ability to function in the workplace, and they are often much more difficult to detect than global deficits in intellectual ability.

Given the substantial variability noted in sometimes very subtle neuropsychological functions in individuals with TSC, even if their overall intellectual ability is in the average to above-average range, it is very important that regular assessments be conducted with these individuals, using developmentally-appropriate neuropsychological assessments, as laid out in the TSC consensus guidelines (de Vries et al., 2005).

## 8. THE PSYCHOSOCIAL LEVEL AND IMPACT OF TAND

Given the life-long complexities of the physical and neuropsychiatric manifestations of TSC, the disorder is associated with a very significant impact on the psychosocial level of individuals, their families, and their communities. For individuals with TSC, self-esteem and self-efficacy is often an area of concern (de Vries, 2010a). The burden on families and parents, in particular, has also been acknowledged. Hallet et al. (2011) performed a systematic review of the burden of disease in TSC focusing on the neurological manifestations and confirmed evidence of high burden, but highlighted that little research has been done on quality of life, burden of care and financial burden (Hallet et al., 2011). In a qualitative study of parental experience and care needs performed in Italy (Graffigna, Bosio, & Cecchini, 2013), in-depth interviews and online discussions with 48 parents of individuals with TSC (aged 1–22) identified three themes. First, a theme of ‘losing control’, with TSC described as an un-understandable and unpredictable disorder making planning for the future very difficult. Second, the theme of ‘coping with the disease’ described stages (akin to the stages of grief) from alarm/confusion, to panic/refusal, anxiety/isolation, to final acceptance/aggregation. In the third theme, the researchers identified a range of ‘unmet needs’, including support towards social integration, psychological support for parents/carers, and for awareness-raising in the community (Graffigna, Bosio, & Cecchini, 2013). These qualitative findings were supported in a US quantitative study of 275 parents/carers of individuals with TSC (Rentz et al., 2015).

An electronic survey of TSAlliance constituents performed in March 2015 included 294 parents/carers and 82 individuals with TSC, mostly from the USA. Of all the aspects of TSC (e.g. epilepsy, skin, kidney etc.), parents/carers and individuals with TSC rated TAND as the second greatest concern, and as the second highest priority for future research after epilepsy in children, and kidney problems in adults (personal communication Steve Roberds, TSAlliance).

It is clear that much further needs to be done to understand and investigate the psychosocial needs of individuals with TSC and their families. However, data are clear that the psychosocial needs require discussion with families, in order to identify suitable support to meet those needs.

## 9. CURRENT RESEARCH AND FUTURE DIRECTIONS

As highlighted in the review, there is some ongoing research in various aspects of TAND and we will highlight just two here. First, as briefly described in section 3 (Behavioural level), there has been significant interest in reducing the complexity of TAND phenomena through ‘bottom-up’ data reduction strategies. Leclezio et al. (2018) showed that it was

feasible to reduce the apparent uniqueness of TAND behaviours to 6 natural clusters. In an extension and replication study, she applied the same methods to >400 individuals with TSC, and confirmed the presence of 7 natural clusters (replicating the 6 previously identified and adding an extra) (unpublished data). Identification of a handful of natural TAND clusters may, in the years to come, become a very helpful clinical strategy to screen, diagnose and treat the otherwise potentially overwhelming manifestations of the disorder (Leclezio & de Vries, 2016; Leclezio, Gardiner-Lubbe, & de Vries, 2018).

Second, there has been growing interest in the potential of mTOR inhibitors to treat TAND manifestations. Apart from the range of indirect pathways to TAND as outlined in this review (e.g. through structural brain abnormalities or seizures), de Vries & Howe proposed that there may also be a direct pathway from mTOR overactivation to TAND (de Vries & Howe, 2007; de Vries, 2010b). Encouraging murine work has supported the possibility that mTOR inhibition may reverse or improve aspects of TAND (Ehninger et al., 2008; Tsai et al., 2012; Waltereit et al., 2011), and have shown that there may be complex combinatorial pathways to TAND (Schneider et al., 2017; Waltereit et al., 2011). Very limited human data exist to date. In the first proof-of-principle study 8 individuals with TSC were monitored for memory and executive skills as part of the TESSTALL renal mTOR inhibitor trial (Davies et al., 2011; de Vries, 2010b). Memory and executive skills improved in some, but not all participants. In a recent phase 2, signal-seeking trial in the USA, a range of TAND-related measures were explored as potential 'signals' for change in response to mTOR inhibitor treatment. After 6 months, only one measure (a behavioural measure of social cognition) favoured everolimus treatment ( $p = 0.011$ ). Strikingly, highly variable individual performance was seen, which made group-based comparisons very hard to interpret (Krueger et al., 2017). A similar trial on adults with TSC (TRON) is currently underway in the UK. Suffice to say, at present, there is no evidence to support the use of mTOR inhibitors as a direct treatment of TAND. However, mTOR inhibitors may well improve TAND and quality of life through the indirect management of, for instance, SEGA, AML or epilepsy, for which these medications have received marketing authorisation in the USA and Europe (Bissler et al., 2013; Franz et al., 2013; French et al., 2016).

In spite of the high frequency and high burden of TAND, many research gaps in TAND remain. At the behavioural level, the wide variability of rates and the relation between behaviours, intellectual ability, gender and genotype would benefit from further work. Also, given the profound impact of many of these manifestations, techniques and measures to help identify the 'function' of behaviours that challenge (e.g. aggression, tantrums, self-injury) would be of immense clinical value, given that functional understanding can lead to targeted interventions (Wilde et al., 2017). At the psychiatric level, much further work on the full range of psychiatric disorders in TSC would be valuable, and in particular, examination of pharmacological and non-pharmacological strategies, in order to generate some evidence-base specific to TSC. Intellectual abilities are clearly highly variable in TSC, and some research on pathways to ID are ongoing. Almost no research has been done on academic difficulties and on interventions to support these, but this is without a doubt, a highly important area for future TSC research. At the neuropsychological level most research has been on animal models and have focused on learning and memory. However, further human neuroscience and animal behavioural work on other neuropsychological domains could also



be invaluable. Many psychosocial interventions exist for a range of psychological conditions. Evaluation of specific intervention programmes specifically aimed at individuals and families who live with TSC may lead to simple but powerful parent training and education programmes with a clear evidence-base.

## 10. CONCLUSION

TSC is associated with a range of physical and neuropsychiatric manifestations. Here we outlined the different levels of TAND (TSC-Associated Neuropsychiatric Disorders) and presented up-to-date information about these levels. Taken together, TAND represents a high frequency, high impact set of manifestations in TSC that is often not identified or treated. Strategies such as annual screening for TAND using the TAND Checklist could be a simple but powerful way towards meeting the TAND needs of individuals with TSC and their families.

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## References

- American Psychiatric Association. Diagnostic and Statistical Manual of Psychiatric Disorders. 5. Arlington, VA: American Psychiatric Publishing; 2013.
- Asato MR, Hardan AY. Neuropsychiatric problems in tuberous sclerosis complex. *Journal of Child Neurology*. 2004; 19(4):241–249. [PubMed: 15163088]
- Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, ... Budde K. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2013; 381(9869):817–824. DOI: 10.1016/S0140-6736(12)61767-X
- Bolton PF, Clifford M, Tye C, Maclean C, Humphrey A, le Marechal K, ... Yates JR. Intellectual abilities in tuberous sclerosis complex: risk factors and correlates from the Tuberous Sclerosis 2000 Study. *Psychological Medicine*. 2015; 45(11):2321–2331. DOI: 10.1017/S0033291715000264 [PubMed: 25827976]
- Bolton PF, Park RJ, Higgins JNP, Griffiths PD, Pickles A. Neuro-epileptic determinants of autism spectrum disorders in tuberous sclerosis complex. *Brain*. 2002; 125(6):1247–1255. [PubMed: 12023313]
- Bruni O, Cortesi F, Giannotti F, Curatolo P. Sleep disorders in tuberous sclerosis: a polysomnographic study. *Brain and Development*. 1995; 17(1):52–56. [PubMed: 7762764]
- Capal JK, Bernardino-Cuesta B, Horn PS, Murray D, Byars AW, Bing NM, Kent B, Pearson DA, Sahin M, Krueger DA. on behalf of the TACERN Study Group. Influence of seizures on early

development in tuberous sclerosis complex. *Epilepsy & Behavior*. 2017; 70:245–252. [PubMed: 28457992]

- Carlisle KW. School factors related to the social and behavioral success of children and adolescents with tuberous sclerosis: Special education placement, services, and parental involvement. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2004; 65(5-B):2666. Full dissertation available online at the University of South Florida Scholar Commons, website: <http://scholarcommons.usf.edu/cgi/viewcontent.cgi?article=2335&context=etd>.
- Chung TK, Lynch ER, Fiser CJ, Nelson DA, Tudor C, Franz DN, Krueger DA. Psychiatric comorbidity and treatment response in patients with tuberous sclerosis complex. *Annals of Clinical Psychiatry*. 2011; 23(4):263–269. [PubMed: 22073383]
- Carrey NJ, MacMaster FP, Gaudet L, Schmidt MH. Striatal creatine and glutamate/glutamine in attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*. 2007; 17(1):11–17. DOI: 10.1089/cap.2006.0008 [PubMed: 17343550]
- Curatolo P, Aronica E, Jansen A, Jansen F, Kotulska K, Lagae L, ... Jozwiak S. Early onset epileptic encephalopathy or genetically determined encephalopathy with early onset epilepsy? Lessons learned from TSC. *European Journal of Paediatric Neurology*. 2016; 20(2):203–211. DOI: 10.1016/j.ejpn.2015.12.005 [PubMed: 26758984]
- Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. *The Lancet*. 2008; 372(9639):657–668. DOI: 10.1016/S0140-6736(08)61279-9
- Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *The Lancet Neurology*. 2015; 14(7):733–745. [PubMed: 26067126]
- Curatolo P, Napolioni V, Moavero R. Autism spectrum disorders in tuberous sclerosis: pathogenetic pathways and implications for treatment. *J Child Neurol*. 2010; 25(7):873–80. DOI: 10.1177/0883073810361789 [PubMed: 20207609]
- Cusmai R, Moavero R, Bombardieri R, Vigeveno F, Curatolo P. Long-term neurological outcome in children with early-onset epilepsy associated with tuberous sclerosis. *Epilepsy & Behavior*. 2011; 22(4):735–739. S1525-5050(11)00501-4 [pii]. [PubMed: 22142783]
- Dabora SL, Jozwiak S, Franz DN, Roberts PS, Nieto A, Chung J, ... Kwiatkowski DJ. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *American Journal of Human Genetics*. 2001; 68(1):64–80. DOI: 10.1086/316951 [PubMed: 11112665]
- D'Agati E, Moavero R, Cerminara C, Curatolo P. Attention-deficit hyperactivity disorder (ADHD) and tuberous sclerosis complex. *Journal of Child Neurology*. 2009; 24(10):1282–1287. [PubMed: 19805824]
- Davies DM, de Vries PJ, Johnson SR, McCartney DL, Cox JA, Serra AL, ... Pointon K. Sirolimus therapy for angiomyolipoma in tuberous sclerosis and sporadic lymphangiomyomatosis: a phase 2 trial. *Clinical Cancer Research*. 2011 clincanres. 0445.2011.
- de Vries PJ. PhD dissertation. University of Cambridge; 2002. The psychopathologies of attention in tuberous sclerosis.
- de Vries PJ. Neurodevelopmental, psychiatric and cognitive aspects of tuberous sclerosis complex. *Tuberous Sclerosis Complex: Genes, Clinical Features and Therapeutics*. 2010a:229–267.
- de Vries PJ. Targeted treatments for cognitive and neurodevelopmental disorders in tuberous sclerosis complex. *Neurotherapeutics*. 2010b; 7(3):275–282. DOI: 10.1016/j.nurt.2010.05.001 [PubMed: 20643380]
- de Vries PJ, Howe CJ. The tuberous sclerosis complex proteins—a GRIPP on cognition and neurodevelopment. *Trends in Molecular Medicine*. 2007; 13(8):319–326. [PubMed: 17632034]
- de Vries PJ, Prather PA. The tuberous sclerosis complex. *The New England Journal of Medicine*. 2007; 356(1):92. author reply 93–94. doi: 10.1056/NEJMc062928
- de Vries PJ, Gardiner J, Bolton PF. Neuropsychological attention deficits in tuberous sclerosis complex (TSC). *American Journal of Medical Genetics Part A*. 2009; 149(3):387–395.
- de Vries PJ, Hunt A, Bolton PF. The psychopathologies of children and adolescents with tuberous sclerosis complex (TSC). *European Child & Adolescent Psychiatry*. 2007; 16(1):16–24. [PubMed: 17268883]

- de Vries PJ, Whittemore VH, Leclezio L, Byars AW, Dunn D, Ess KC, ... Jansen A. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. *Pediatric Neurology*. 2015; 52(1):25–35. [PubMed: 25532776]
- 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 & Adolescent Psychiatry*. 2005; 14(4):183–190. [PubMed: 15981129]
- Eden KE, de Vries PJ, Moss J, Richards C, Oliver C. Self-injury and aggression in tuberous sclerosis complex: cross syndrome comparison and associated risk markers. *Journal of Neurodevelopmental Disorders*. 2014; 6(1):10. [PubMed: 24822087]
- Ehninger D, Han S, Shilyansky C, Zhou Y, Li W, Kwiatkowski DJ, ... Silva AJ. Reversal of learning deficits in a *Tsc2*<sup>+/-</sup> mouse model of tuberous sclerosis. *Nature Medicine*. 2008; 14(8):843–848. DOI: 10.1038/nm1788
- Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, ... Jozwiak S. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2013; 381(9861):125–132. DOI: 10.1016/S0140-6736(12)61134-9 [PubMed: 23158522]
- French JA, Lawson JA, Yapici Z, Ikeda H, Polster T, Nabbout R, ... Franz DN. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016; 388(10056):2153–2163. DOI: 10.1016/S0140-6736(16)31419-2 [PubMed: 27613521]
- Gillberg IC, Gillberg C, Ahlsen G. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. *Developmental Medicine & Child Neurology*. 1994; 36(1):50–56. [PubMed: 8132114]
- Goh S, Kwiatkowski DJ, Dorer DJ, Thiele EA. Infantile spasms and intellectual outcomes in children with tuberous sclerosis complex. *Neurology*. 2005; 65(2):235–238. DOI: 10.1212/01.wnl.0000168908.78118.99 [PubMed: 16043792]
- Graffigna G, Bosio C, Cecchini I. Assisting a child with tuberous sclerosis complex (TSC): a qualitative deep analysis of parents' experience and caring needs. *BMJ Open*. 2013; 3(12):e003707.doi: 10.1136/bmjopen-2013-003707
- Hallett L, Foster T, Liu Z, Blieden M, Valentim J. Burden of disease and unmet needs in tuberous sclerosis complex with neurological manifestations: systematic review. *Current Medical Research and Opinion*. 2011; 27(8):1571–1583. [PubMed: 21692602]
- Harrison JE, O'Callaghan FJ, Hancock E, Osborne JP, Bolton PF. Cognitive deficits in normally intelligent patients with tuberous sclerosis. *American Journal of Medical Genetics*. 1999; 88(6):642–646. [PubMed: 10581483]
- Henske EP, Jozwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. *Nature Reviews Disease Primers*. 2016; 2:16035.doi: 10.1038/nrdp.2016.35
- Huang CH, Peng SSF, Weng WC, Su YN, Lee WT. The relationship of neuroimaging findings and neuropsychiatric comorbidities in children with tuberous sclerosis complex. *Journal of the Formosan Medical Association*. 2015; 114(9):849–854. [PubMed: 24698169]
- Humphrey A, MacLean C, Ploubidis GB, Granader Y, Clifford M, Haslop M. ... Tuberous Sclerosis Study Group. Intellectual development before and after the onset of infantile spasms: a controlled prospective longitudinal study in tuberous sclerosis. *Epilepsia*. 2014; 55(1):108–116. DOI: 10.1111/epi.12484 [PubMed: 24417555]
- Humphrey A, Neville BG, Clarke A, Bolton PF. Autistic regression associated with seizure onset in an infant with tuberous sclerosis. *Developmental Medicine & Child Neurology*. 2006; 48(7):609–611. DOI: 10.1017/S0012162206001277 [PubMed: 16780633]
- Hunt A. Development, behaviour and seizures in 300 cases of tuberous sclerosis. *Journal of Intellectual Disability Research*. 1993; 37(Pt 1):41–51. [PubMed: 7681710]
- Hunt A. A comparison of the abilities, health and behaviour of 23 people with tuberous sclerosis at age 5 and as adults. *Journal of Applied Research in Intellectual Disabilities*. 1998; 11(3):227–238.
- Hunt A, Stores G. Sleep disorder and epilepsy in children with tuberous sclerosis: a questionnaire-based study. *Developmental Medicine & Child Neurology*. 1994; 36(2):108–115. [PubMed: 7510655]

- Jambaque I, Cusmai R, Curatolo P, Cortesi F, Perrot C, Dulac O. Neuropsychological aspects of tuberous sclerosis in relation to epilepsy and MRI findings. *Developmental Medicine & Child Neurology*. 1991; 33(8):698–705. [PubMed: 1916024]
- Jansen FE, Vincken KL, Algra A, Anbeek P, Braams O, Nellist M, ... van Nieuwenhuizen O. Cognitive impairment in tuberous sclerosis complex is a multifactorial condition. *Neurology*. 2008; 70(12):916–923. DOI: 10.1212/01.wnl.0000280579.04974.c0 [PubMed: 18032744]
- Jeste SS, Sahin M, Bolton P, Ploubidis GB, Humphrey A. Characterization of autism in young children with tuberous sclerosis complex. *Journal of Child Neurology*. 2008; 23(5):520–525. [PubMed: 18160549]
- Jeste SS, Varcin KJ, Helleman GS, Gulsrud AC, Bhatt R, Kasari C, ... Nelson CA. Symptom profiles of autism spectrum disorder in tuberous sclerosis complex. *Neurology*. 2016; 87(8):766–772. [PubMed: 27440144]
- Jeste SS, Wu JY, Senturk D, Varcin K, Ko J, McCarthy B, ... Nelson CA 3rd. Early developmental trajectories associated with ASD in infants with tuberous sclerosis complex. *Neurology*. 2014; 83(2):160–168. DOI: 10.1212/WNL.0000000000000568 [PubMed: 24920850]
- Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. *Psychological Medicine*. 2003; 33(2):335–344. [PubMed: 12622312]
- Jones AC, Daniells CE, Snell RG, Tachataki M, Idziaszczyk SA, Krawczak M, ... Cheadle JP. Molecular genetic and phenotypic analysis reveals differences between TSC1 and TSC2 associated familial and sporadic tuberous sclerosis. *Human Molecular Genetics*. 1997; 6(12):2155–2161. [PubMed: 9328481]
- Kilincaslán A, Kok BE, Tekturk P, Yalcinkaya C, Ozkara C, Yapici Z. Beneficial Effects of Everolimus on Autism and Attention-Deficit/Hyperactivity Disorder Symptoms in a Group of Patients with Tuberous Sclerosis Complex. *Journal of Child and Adolescent Psychopharmacology*. 2017; 27(4):383–388. DOI: 10.1089/cap.2016.0100 [PubMed: 27797585]
- Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, ... de Vries PJ. Tuberous Sclerosis registry to increase disease Awareness (TOSCA)—baseline data on 2093 patients. *Orphanet Journal of Rare Diseases*. 2017; 12(1):2. [PubMed: 28057044]
- Kothare SV, Singh K, Chalifoux JR, Staley BA, Weiner HL, Menzer K, Devinsky O. Severity of manifestations in tuberous sclerosis complex in relation to genotype. *Epilepsia*. 2014; 55(7):1025–1029. DOI: 10.1111/epi.12680 [PubMed: 24917535]
- Krueger DA, Northrup H, Roberds S, Smith K, Sampson J, Korf B, ... Povey S. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013; 49(4):255–265. [PubMed: 24053983]
- Krueger DA, Sadhwani A, Byars AW, de Vries PJ, Franz DN, Whittemore VH, ... Sahin M. Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders. *Annals of Clinical and Translational Neurology*. 2017; 4(12):877–887. DOI: 10.1002/acn3.494 [PubMed: 29296616]
- Leclezio L, de Vries PJ. Advances in the treatment of tuberous sclerosis complex. *Current Opinion in Psychiatry*. 2015; 28(2):113–120. [PubMed: 25602245]
- Leclezio L, Gardner-Lubbe S, de Vries PJ. Is It Feasible to Identify Natural Clusters of TSC-Associated Neuropsychiatric Disorders (TAND)? *Pediatric Neurology*. 2018
- Leclezio L, Jansen A, Whittemore VH, de Vries PJ. Pilot validation of the tuberous sclerosis-associated neuropsychiatric disorders (TAND) checklist. *Pediatric Neurology*. 2015; 52(1):16–24. [PubMed: 25499093]
- Lewis J, Thomas H, Murphy K, Sampson J. Genotype and psychological phenotype in tuberous sclerosis. *Journal of Medical Genetics*. 2004; 41(3):203–207. [PubMed: 14985384]
- Moavero R, Napolitano A, Cusmai R, Vigeveno F, Figa-Talamanca L, Calbi G, ... Bernardi B. White matter disruption is associated with persistent seizures in tuberous sclerosis complex. *Epilepsy & Behavior*. 2016; 60:63–67. DOI: 10.1016/j.yebeh.2016.04.026 [PubMed: 27179194]

- Moss J, Oliver C, Nelson L, Richards C, Hall S. Delineating the profile of autism spectrum disorder characteristics in Cornelia de Lange and fragile X syndromes. *American Journal on Intellectual and Developmental Disabilities*. 2013; 118(1):55–73. [PubMed: 23301903]
- Muzykewicz DA, Newberry P, Danforth N, Halpern EF, Thiele EA. Psychiatric comorbid conditions in a clinic population of 241 patients with tuberous sclerosis complex. *Epilepsy & Behavior*. 2007; 11(4):506–513. S1525-5050(07)00253-3 [pii]. [PubMed: 17936687]
- Northrup H, Krueger DA, Roberds S, Smith K, Sampson J, Korf B, ... Povey S. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatric Neurology*. 2013; 49(4):243–254. [PubMed: 24053982]
- Numis AL, Major P, Montenegro MA, Muzykewicz DA, Pulsifer MB, Thiele EA. Identification of risk factors for autism spectrum disorders in tuberous sclerosis complex. *Neurology*. 2011; 76(11):981–987. 76/11/981 [pii]. DOI: 10.1212/WNL.0b013e3182104347 [PubMed: 21403110]
- Ogdie MN, Fisher SE, Yang M, Ishii J, Francks C, Loo SK, ... Nelson SF. Attention deficit hyperactivity disorder: fine mapping supports linkage to 5p13, 6q12, 16p13, and 17p11. *American Journal of Human Genetics*. 2004; 75(4):661–668. DOI: 10.1086/424387 [PubMed: 15297934]
- Pliszka S. AACAP Work Group of Quality Issues. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007; 46(7):894–921. DOI: 10.1097/chi.0b013e318054e724 [PubMed: 17581453]
- Prabowo AS, Anink JJ, Lammens M, Nellist M, van den Ouweland AM, Adle-Biassette H, ... Aronica E. Fetal brain lesions in tuberous sclerosis complex: TORC1 activation and inflammation. *Brain Pathology*. 2013; 23(1):45–59. DOI: 10.1111/j.1750-3639.2012.00616.x [PubMed: 22805177]
- Prather P, de Vries PJ. Behavioral and cognitive aspects of tuberous sclerosis complex. *Journal of Child Neurology*. 2004; 19(9):666–674. [PubMed: 15563012]
- Pulsifer MB, Winterkorn EB, Thiele EA. Psychological profile of adults with tuberous sclerosis complex. *Epilepsy & Behavior*. 2007; 10(3):402–406. [PubMed: 17392032]
- Rentz AM, Skalicky AM, Pashos CL, Liu Z, Magestro M, Pelletier CL, ... Dunn DW. Caring for children with tuberous sclerosis complex: what is the physical and mental health impact on caregivers? *Journal of Child Neurology*. 2015; 30(12):1574–1581. [PubMed: 25838447]
- Ridler K, Suckling J, Higgins N, De Vries P, Stephenson C, Bolton P, Bullmore E. Neuroanatomical correlates of memory deficits in tuberous sclerosis complex. *Cerebral Cortex*. 2006; 17(2):261–271. [PubMed: 16603714]
- Sancak O, Nellist M, Goedbloed M, Elfferich P, Wouters C, Maat-Kievit A, ... van den Ouweland A. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype-phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. *European Journal of Human Genetics*. 2005; 13(6):731–741. DOI: 10.1038/sj.ejhg.5201402 [PubMed: 15798777]
- Schneider M, de Vries PJ, Schonig K, Rossner V, Waltereit R. mTOR inhibitor reverses autistic-like social deficit behaviours in adult rats with both Tsc2 haploinsufficiency and developmental status epilepticus. *European Archives of Psychiatry and Clinical Neuroscience*. 2017; 267(5):455–463. DOI: 10.1007/s00406-016-0703-8 [PubMed: 27263037]
- Tierney KM, McCartney DL, Serfontein JR, de Vries PJ. Neuropsychological attention skills and related behaviours in adults with tuberous sclerosis complex. *Behavior Genetics*. 2011; 41(3):437–444. [PubMed: 21191642]
- Trickett J, Heald M, Oliver C, Richards C. A cross-syndrome cohort comparison of sleep disturbance in children with Smith-Magenis syndrome, Angelman syndrome, autism spectrum disorder and tuberous sclerosis complex. *Journal of Neurodevelopmental Disorders*. 2018; 10(1):9. [PubMed: 29490614]
- Tsai PT, Hull C, Chu Y, Greene-Colozzi E, Sadowski AR, Leech JM, ... Sahin M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature*. 2012; 488(7413):647–651. DOI: 10.1038/nature11310 [PubMed: 22763451]
- Turic D, Langley K, Mills S, Stephens M, Lawson D, Govan C, ... Thapar A. Follow-up of genetic linkage findings on chromosome 16p13: evidence of association of N-methyl-D aspartate

- glutamate receptor 2A gene polymorphism with ADHD. *Molecular Psychiatry*. 2004; 9(2):169–173. DOI: 10.1038/sj.mp.4001387 [PubMed: 14966475]
- van Eeghen AM, Black ME, Pulsifer MB, Kwiatkowski DJ, Thiele EA. Genotype and cognitive phenotype of patients with tuberous sclerosis complex. *European Journal of Human Genetics*. 2012; 20(5):510–515. DOI: 10.1038/ejhg.2011.241 [PubMed: 22189265]
- van Eeghen AM, Chu-Shore CJ, Pulsifer MB, Camposano SE, Thiele EA. Cognitive and adaptive development of patients with tuberous sclerosis complex: a retrospective, longitudinal investigation. *Epilepsy & Behavior*. 2012; 23(1):10–15. DOI: 10.1016/j.yebeh.2011.10.005 [PubMed: 22099526]
- Waltereit R, Japs B, Schneider M, de Vries PJ, Bartsch D. Epilepsy and Tsc2 haploinsufficiency lead to autistic-like social deficit behaviors in rats. *Behavior Genetics*. 2011; 41(3):364–372. DOI: 10.1007/s10519-010-9399-0 [PubMed: 20927644]
- Wilde L, Eden K, de Vries P, Moss J, Welham A, Oliver C. Self-injury and aggression in adults with tuberous sclerosis complex: Frequency, associated person characteristics, and implications for assessment. *Research in Developmental Disabilities*. 2017; 64:119–130. [PubMed: 28411579]
- Wilde L, Wade K, Eden K, Moss J, Vries P, Oliver C. Persistence of self-injury, aggression and property destruction in children and adults with tuberous sclerosis complex. *Journal of Intellectual Disability Research*. 2018
- Wong HT, McCartney DL, Lewis JC, Sampson JR, Howe CJ, de Vries PJ. Intellectual ability in tuberous sclerosis complex correlates with predicted effects of mutations on TSC1 and TSC2 proteins. *Journal of Medical Genetics*. 2015; 52(12):815–822. DOI: 10.1136/jmedgenet-2015-103154 [PubMed: 26408672]
- World Health Organization. *International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10)*. Geneva: World Health Organization; 1992.



**Table 1**

## TSC-Associated Neuropsychiatric Disorders (TAND) – levels of investigation

Level	Name	Description	Examples
Level 1	Behavioral 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 etc.
Level 2	Psychiatric Level	This level is defined by psychiatric diagnostic classification systems such as DSM-5 or ICD-10. At this level the clinician determines whether behaviours observed at level 1 meet criteria for specific psychiatric disorders.	Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Anxiety Disorder, Depressive Disorder
Level 3	Intellectual Level	This level measures intellectual ability as defined by standardized IQ-type measures.	Mild, Moderate, Severe or Profound Intellectual Disability (ID)
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 standardized 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, 5<sup>th</sup> Edition (APA, 2013)

ICD-10 = International Classification of Diseases and Related Health Problems, 10<sup>th</sup> Edition (WHO, 1992)

**Table 2**

Examples of the range of reported rates of behavioural difficulties in Tuberous Sclerosis Complex (and sample characteristics)

Behaviour	Rate estimate	
	Lower	Higher
Depressed mood	19% (adults, able to self-report) (Lewis, Thomas, Murphy, & Sampson, 2004)	43 % (adults, able to self-report) (Pulsifer, Winterkorn, & Thiele, 2007)
Anxiety	41% (adults, able to self-report) (Pulsifer et al., 2007)	56% (adults, able to self-report) (Lewis et al., 2004)
Self-injury	17% (children and adolescents, no ID) (de Vries, Hunt, & Bolton, 2007)	69% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Aggressive outbursts	37% (adults, ID)(Wilde et al., 2017)	66% (children and adolescents, mild-moderate ID) (de Vries, Hunt, & Bolton, 2007)
Temper tantrums	47% (children and adolescents, no ID) (de Vries, Hunt, & Bolton, 2007)	70% (children and adolescents, mild-moderate ID) (de Vries, Hunt, & Bolton, 2007)
Poor eye contact	23% (children and adolescents, no ID) (de Vries, Hunt, & Bolton, 2007)	71% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Repetitive and ritualistic behaviours	20% (children and adolescents, no ID) (de Vries, Hunt, & Bolton, 2007)	83% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Speech and language delay	32% (children and adolescents, no ID)(de Vries, Hunt, & Bolton, 2007)	86% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Overactivity/hyperactivity	22% (adults, ID) (Hunt, 1998)	73% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Impulsivity	36% (children and adolescents, no ID) (de Vries, Hunt, & Bolton, 2007)	62% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)
Sleep difficulties	15% (children and adolescents, ID and no ID) (Trickett, Heald, Oliver, & Richards, 2018)	74% (children and adolescents, severe-profound ID) (de Vries, Hunt, & Bolton, 2007)

ID = Intellectual Disability