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 behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties, which are often under-diagnosed and undertreated. 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 counselors, pediatricians, 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

ADHD, anxiety, autism spectrum disorder, behavior, depression, mental health, neuropsychological deficits, scholastic difficulties, TANDTSC

1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is a multisystem 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, Joziwak, Kingswood, Sampson, & Thiele, 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, & Joziwak, 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 et al., 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, 2010a; de Vries et al., 2005; de Vries et al., 2015). The neurological and neuropsychiatric features of TSC lead to the greatest burden of disease (Curatolo et al., 2015; Hallett, Foster, Liu, Blidden, & Valentim, 2011; Rentz et al., 2015). Although there has been great progress in the identification and treatment of many of
the physical features of TSC, including subependymal giant cell astrocytoma (SEGA), angiomyolipoma (AML), and epilepsy, the neuropsychiatric manifestations remain highly underidentified and undertreated (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 counselors, pediatricians, 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" as an umbrella term to include the full range of neurodevelopmental, behavioral, 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 multiprofessional (e.g., multiple health professionals such as psychiatry, psychology, occupational therapy, and speech and language pathology) and transdisciplinary (e.g., from health, education, and social care systems involving physicians, educators, and social workers) input, as well as collaboration with a range of other statutory and nonstatutory organizations. Across all these professions and sectors, different "language" has been used to refer to various aspects of development, mental health, or psychosocial needs. To generate a "shared language" that might aid interprofessional communication and to guide future research, the panel defined six "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. 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 organizations 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 summarize current evidence for each of the TAND levels of investigation, including basic guidelines for further evaluation and intervention.

3 | THE BEHAVIORAL LEVEL

The behavioral level of TAND consists of behaviors 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 onward for psychological or psychiatric assessment. The largest dataset including behavioral 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 behavioral problem, with overactivity, impulsivity, and sleeping difficulties being the most common behavioral 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 behaviors were reported in 6–8% of individuals (Kingswood et al., 2017). Estimated rates of TAND behavioral 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 behaviors, 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 lower reported rates identified in TOSCA suggested that, even in TOSCA participating centers, TAND manifestations were typically underidentified and undertreated (Kingswood et al., 2017). Table 2 (updated and expanded from Leclerc & de Vries, 2016) illustrates the variability in estimates of rates of TAND behaviors 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 the work of de Vries et al. (2007). In contrast to most behavioral problems in TSC, those relating to low mood and anxiety do not seem to be different between those with and without ID (de Vries et al., 2007). Therefore, all carers and professionals should 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 behavioral symptomatology relating to mood may be underestimated. Therefore, it is important that appropriate tools, such as the TAND Checklist (de Vries et al., 2015), are used to evaluate and monitor these behavioral features of TAND.

Upper estimates, all from children and adolescents with ID (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 et al., 2007), and also in adults who have ID (Wilde et al., 2017), suggesting that this behavior is sensitive to gains in both age and ability. Children with severe ID are therefore a particularly high-risk group for this deleterious behavioral 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 et al., 2007), although aggressive outbursts also seem 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 et al., 2007; Eden, de Vries, Moss, Richards, & Oliver, 2014). This suggests that childhood might be a high-risk time for aggressive behavior 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 behavioral 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 behavioral difficulties in social communication in children and adolescents with TSC are associated with level of intellectual ability (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 behaviors, both children above and below diagnostic thresholds for ASD are reported to have specific deficits in imaginative play skills (Jeste et al., 2008). For children who exceed ASD thresholds, toddlers with TSC and ASD are reported to demonstrate social communication behaviors 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 behaviors (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 behavioral 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 correlate strongly with the presence or absence of ID (de Vries et al., 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 behaviors 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 behavioral 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 et al., 2018) are supported by direct polysomnography assessment in children with TSC, which found shorter total sleep duration (Bruni, Cortesi, Giannotti, & Curatolo, 1995). Other sleep behavior 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. Furthermore, an association between sleep difficulties and daytime overactivity/impulsivity may suggest that intervening for poor sleep could improve other behavioral difficulties in TSC (Trickett et al., 2018).

The diversity of the behavioral manifestations of TSC and the variable influence of age and ability and interactions between behaviors 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, 2016). Identifying clusters of TAND behaviors may help to reduce this complexity. Although there are “top-down” groupings of these TAND behaviors (e.g., relating to psychiatric diagnostic categories), there has never been an exploration of the natural grouping of the behavioral manifestations of TSC until recently. A feasibility study of identifying natural TAND clusters found six clusters, of which four included the majority of behavioral variables (Leclezio et al., 2018). These were “ASD-like” (delayed language, repetitive behavior, difficulties with eating, and self-injury), “behavioral dysregulation” (temper tantrums, mood swings, and aggressive outbursts), “hyperactive/impulsive” (overactivity, restlessness, and impulsivity), and “mood/anxiety” (anxiety, depressed mood, and sleep difficulties). This suggests potential for a more streamlined approach to understanding and evaluating TAND behaviors for both families and professionals, which may in turn reduce treatment paralysis in TSC and improve outcomes for those experiencing behavioral 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

4.1.1 | Autism spectrum disorder

TSC represents one of the major single gene disorders causing autism spectrum disorder (ASD) (Curatolo et al., 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 et al., 2015). Potential factors increasing the risk for ASD include TSC gene mutations, structural brain abnormalities, and epilepsy. Although a prediction of the behavioral 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, tuberbrain 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 multicomponential 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, Napolioli, & Moavero, 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 mammalian/mechanistic Target of Rapamycin (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 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 multicenter study is now ongoing trying to answer this question such as the EPITOP (www.clinicaltrials.gov) and PREVENT trials (www.clinicaltrials.gov NCT02098759 and 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 et al., 2008). After the second year of life, abnormal behaviors including hyperactivity, rituals, repetitive behaviors, and temper tantrums can appear (Jeste et al., 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 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 et al., 2017; Tsai et al., 2012; Waltereit et al., 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), but no clinical recommendations about mTOR inhibitors for ASD in TSC can be made to date.

4.1.2 Attention deficit hyperactivity disorder (ADHD)
ADHD occurs in about 30–50% of subjects with TSC (de Vries et al., 2007; Gillberg, Gillberg, & Ahlsen, 1994; Hunt, 1993; Muzykewicz, Newberry, Danforth, Halpern, & Thiele, 2007) thus being 10 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 in 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 behavioral level, there have been relatively few studies of anxiety and depressive disorders in TSC. Lewis and colleagues (Lewis et al., 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 and TSC2 in relation to anxiety or depressive disorder; however, the Muzykewicz data found a significant correlation with TSC2 status. Therefore, this question clearly still requires further examination before any firm conclusions can be drawn.

The TuberOus SClerosis registry to increase disease Awareness (TOSCA) 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. Although importantly, TOSCA did identify infants and children with anxiety disorders, emphasizing 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 and 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 behaviors, as discussed under the behavioral 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 behaviors are very common in association with ASD in TSC. Therefore, clinicians should 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 et al., 2007; Gillberg et al., 1994; Goh, Kwiatkowski, Dorer, & 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 and 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 et al., 2012). However, Wong et al. (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 et al., 2012), poor seizure control (Goh et al., 2005; van Eeghen et al., 2012), and use of more antiepileptic medications likely reflecting more problematic seizure control (van Eeghen 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 (ISs), to a mean IQ of 73 after exposure to IS for less than 1 month, to a mean IQ = 62 after exposure to IS for more than 1 month. The presence of TSC2 mutations has 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 101 individuals with known TSC mutations who were all assessed using a range of standardized 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 of 66 showing significant improvement and 11 of 66 showing significant deterioration. In contrast, there was a significant decline over time in adaptive behavior 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 stabilizes 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 et al., 2007; Joinson et al., 2003). Interestingly, van Eeghen 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 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 the presence of ID has been associated with a higher risk for a range of behavioral manifestations (see also discussion under the “behavioral level”) including ASD-related (poor eye contact, repetitive behaviors) and ADHD-related (overactivity, restlessness, and 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 standardized 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.” Jambaqué 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 >2,000 individuals with TSC (Kingswood et al., 2017), participants were asked how many 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 and 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 less than 5th 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, for example, doing a visual search task while listening for an auditory cue (de Vries, 2002; de Vries et al., 2009; Tierney et al., 2011). Although dual-task deficits have been proposed as a potential neuropsychological “signature” of TSC (de Vries, 2002; Tierney et al., 2011), it should be noted that there is considerable variability between individuals with TSC with respect to specific attention deficits (de Vries et al., 2009). Importantly, attention deficits have strong correlations with real-life difficulties, academic performance, and a sense of feeling overwhelmed (Tierney et al., 2011). These neuropsychological deficits, however, do not necessarily correlate with behavioral attentional rating scales such as those used in ADHD (de Vries et al., 2009). For this reason all individuals with TSC should be considered at high risk for neuropsychological attention deficits, not only those with behavioral 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; Jambaqué 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 <5th percentile) in one or more areas, whereas 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 behaviors have also been noted in adults with TSC (Curatolo et al., 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 behaviors 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 are often an area of concern (de Vries, 2010a). The burden on families and parents, in particular, has also been acknowledged. Hallett 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 (Hallett 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 toward social integration, psychological support for parents/carers, and for awareness-raising in the community (Graffigna et al., 2013). These qualitative findings were supported in a U.S. 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 United States. Of all the aspects of TSC (e.g., epilepsy, skin, and kidney), 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 (S. Roberds, personal communication, TSAlliance, 15 July 2015).

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, 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, 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 behaviors to six natural clusters. In an extension and replication study, she applied the same methods to >400 individuals with TSC and confirmed the presence of seven natural clusters (replicating the six 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 et al., 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 and Howe proposed that there may also be a direct pathway from mTOR overactivation to TAND (de Vries, 2010b; de Vries & Howe, 2007). 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, eight 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 United States, 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 behavioral measure of social cognition) favored 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 United Kingdom. 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 authorization in the United States 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 behavioral level, the wide variability of rates and the relation between behaviors, 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 behaviors 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 nonpharmacological strategies, 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 has focused on learning and memory. However, further human neuroscience and animal behavioral work on other neuropsychological domains could also be invaluable. Many psychosocial interventions exist for a range of psychological conditions. Evaluation of specific intervention programs specifically aimed at individuals and families who live with TSC may lead to simple but powerful parent training and education programs 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 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 toward meeting the TAND needs of individuals with TSC and their families.

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