Neuropsychological Attention Skills and Related Behaviours in Adults with Tuberous Sclerosis Complex

Article *in* Behavior Genetics · December 2010

DOI: 10.1007/s10519-010-9423-4 · Source: PubMed

4 authors, including:

Jaco Serfontein
Cambridgeshire and Peterborough NHS Foundation Trust
14 PUBLICATIONS **170** CITATIONS
SEE PROFILE

Petrus de Vries
University of Cape Town
278 PUBLICATIONS **15,438** CITATIONS
SEE PROFILE

Behav Genet (2011) 41:437–444
DOI 10.1007/s10519-010-9423-4

ORIGINAL RESEARCH

Neuropsychological Attention Skills and Related Behaviours in Adults with Tuberous Sclerosis Complex

Kevin M. Tierney · Deborah L. McCartney · Jaco R. Serfontein · Petrus J. de Vries

Received: 2 September 2010 / Accepted: 30 November 2010 / Published online: 30 December 2010

Abstract Tuberous sclerosis complex (TSC) is a genetic disorder associated with mTOR over-activation and disruption of MAPK, PI3K and AMPK signalling. Children with TSC have significant deficits on neuropsychological attention tasks, particularly dual tasking. Here we investigated attentional skills and related behaviours in daily life in normally intelligent adults with TSC and matched controls using the Test of Everyday Attention for Children (TEA-Ch) and the Attention-Deficit Scales for Adults (ADSA). No group differences were demonstrated on selective or sustained attention tasks carried out alone. However, adults with TSC performed significantly worse when these tasks were combined in a cross-modal dual task condition. On the ADSA the TSC group had significantly worse scores on several subscales (attention/concentration, behaviour/disorganization, academic and emotional behaviours) compared to controls and these correlated with dual task performance, indicating a clear impact of dual task deficits on attention-related behaviours in daily life. The presence or absence of epilepsy did not influence dual task performance or attention-deficits in daily life. Taken together with similar findings in children, results suggest that dual task difficulties are a core feature of the neuropsychological phenotype of TSC.

Keywords Dual-tasking · Neurodevelopmental disorders · TEA-Ch · Attention-Deficit Scales for Adults · Mammalian target of rapamycin · mTOR

Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder with multi-system involvement that includes significant neuropsychiatric manifestations such as epilepsy, autism, Attention-Deficit/Hyperactivity Disorder (ADHD), intellectual disability and specific cognitive impairments (de Vries et al. 2005, 2009; Prather and de Vries 2004). TSC occurs as a spontaneous mutation in approximately 70% of cases, and as an inherited autosomal-dominant condition in the remaining 30% of cases (Crino et al. 2006). It affects approximately 1 in 6,000 people (Osborne et al. 1991). The disorder is caused by mutations in either of two genes, the *TSC1* gene, on chromosome 9q34, or the *TSC2* gene, on chromosome 16p13.3 (Povey et al. 1994). Thousands of unique TSC mutations have been identified (http://chromium.liacs.nl/LOVD2/TSC/home.php; Kwiatkowski 2010). The TSC1–TSC2 protein complex acts as a molecular switchboard integrating a number of intracellular signalling cascades, including the AMPK, PI3K and MAPK pathways.

Edited by Pierre Roubertoux.

K. M. Tierney · P. J. de Vries
Neurodevelopmental Service (NDS), Cambridgeshire and Peterborough NHS Foundation Trust, Peterborough, UK

D. L. McCartney · P. J. de Vries (✉)
Developmental Psychiatry Section, Douglas House, University of Cambridge, 18b Trumpington Road, Cambridge CB2 8AH, UK
e-mail: pd215@cam.ac.uk

D. L. McCartney
Department of Medical Genetics, Cardiff University, Cardiff, UK

J. R. Serfontein
Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

A mutation in either *TSC1* or *TSC2* may disrupt the TSC1–TSC2 complex, resulting in over-activation of mTOR (mammalian target of rapamycin) signalling (Crino et al. 2006; Curatolo et al. 2008; de Vries and Howe 2007). Interestingly, examination of the evolution of the TSC1/TSC2-TOR signalling pathway showed that the pathway was built up from a simpler one, present in the ancestral eukaryote, which coupled cell growth and energy supplies. Additional elements such as TSC1 and TSC2 were "bolted on" only in particular eukaryotic lineages (Serfontein et al. 2010). Examination of structural and functional domains of TSC1 and TSC2 across commonly used animal models, such as rat, mouse, zebrafish and fruit fly, suggests that the TSC proteins show high similarity only in some of these models. Caution should therefore be exercised when interpreting findings from some of these model organisms (Serfontein et al. in press).

There is a wide variability in cognitive and behavioural phenotypes in people with TSC (de Vries 2010; de Vries and Prather 2007; Prather and de Vries 2004). This variability is clearly seen in the range of global intellectual abilities seen in the disorder. The emerging consensus is that TSC has at least two distinct cognitive endophenotypes (de Vries and Prather 2007; Prather and de Vries 2004; Joinson et al. 2003). Approximately 70% of people with TSC have global intellectual functioning which is consistent with the normal distribution of IQ indices, although with a mean IQ slightly lower than seen in the general population (normal distribution phenotype). The remaining 30% of people with TSC do not fit the expected normal distribution, and have profound intellectual disabilities (profound phenotype). The causes of intellectual disability in TSC have not been fully delineated, and the most commonly researched factors (tuber size and location, seizures and *TSC1* vs. *TSC2* mutation) show some association with global intellectual ability but appear to be neither necessary nor sufficient to explain the wide variation in global intellectual abilities (de Vries 2010; Jansen et al. 2008; de Vries and Prather 2007). Recently, a molecular model of cognitive and behavioural outcomes in TSC was proposed which may go further in explaining the variation in neurocognitive manifestations of the condition (de Vries and Howe 2007). The molecular model is supported by evidence of learning and behavioural deficits in TSC animal models in the absence of structural brain lesions or seizures (de Vries and Howe 2007; Ehninger et al. 2008; Goorden et al. 2007; Waltereit et al. 2006, 2011; Ehninger and Silva 2011).

There is growing evidence that even individuals with TSC who have normal intellectual development have specific impairments in several cognitive domains. Impairment, as defined by neuropsychological convention, refers to performance two or more standard deviations (SD) below the mean performance. Studies that have assessed normally intelligent adults with TSC have identified significantly poorer performance on tasks that are designed to tap executive control processes and memory abilities (Harrison et al. 1999; Ridler et al. 2007). Children with TSC have been found to have impairments in executive functioning, visuospatial skills and language (for reviews refer, de Vries 2010). Of these areas of specific cognitive impairment executive deficits were the most frequently observed, affecting approximately two-thirds of participants (Prather et al. 2006). In a study specifically assessing attentional skills using the TEA-Ch (Manly et al. 1999; Manly et al. 2001), de Vries and colleagues observed that children with TSC in the normal distribution phenotype had significant difficulties compared to unaffected siblings on tests of selective attention, sustained attention and dual tasking (de Vries et al. 2009). In particular, 17 of the 20 children with TSC performed in the clinically impaired range on one or both of the unimodal and cross-modal dual task tests (12 of the 15 children with an IQ above 70 were impaired on at least one of these tasks). Despite the high prevalence of attention deficits in children, no study has specifically looked at attentional abilities in adults with TSC.

Considering the high frequency of attention and executive control problems observed in children with TSC, it could be predicted that TSC is associated with difficulties in behaviour in daily life. Several epidemiological studies of TSC in children have noted the high incidence of attention-deficit/hyperactivity disorder, with the estimated rate for children without global intellectual impairment falling in the 30–55% range (Gillberg et al. 1993; de Vries et al. 2007). Unfortunately, no systematic studies of attention deficit type behaviours have been carried out in adults with TSC. At a clinical level, many normally intelligent adults with TSC report poor concentration, impulsivity, poor organisation and feeling easily overwhelmed when having to 'multi-task' (de Vries unpublished data). These difficulties can cause problems in daily functioning, even when they do not meet the threshold for a formal diagnosis of ADHD.

The current study investigated neuropsychological attentional skills in a sample of adults with TSC with intelligence indices in the normal range. The primary research question was whether adults with TSC have difficulties in performing neuropsychological tests of attention. Secondly, this study aimed to ascertain whether any attentional impairments found were associated with impaired attention-related behaviours in daily life. We hypothesised that adults with TSC would be impaired on attentional skills, particularly dual tasking as this was the most common area of impairment in children and adolescents with TSC (de Vries et al. 2009).

Method

Participants

This study was part of a larger project investigating brain substrates of neuropsychological deficits in TSC, conducted with ethical approval from the Thames Valley Medical Research Ethics Committee (03/12/047), the Cambridge Local Research Ethics Committee (04/035M) and with R&D approval of the Cambridgeshire and Peterborough NHS Foundation Trust. Participants for this study were recruited through the Tuberous Sclerosis Association (TSA) UK. All participants gave informed written consent. Participants were reimbursed for attendance expenses and were given a small gratuity for participating.

Twenty-five adults with a confirmed clinical diagnosis of TSC (Roach et al. 1998) agreed to participate. Three participants had performance IQs (PIQ) below 80 and were excluded. One participant was excluded from this study as she was unwilling to complete the neuropsychological assessments. Of the remaining 21 adults with TSC, seven had never had a seizure, three had seizures in childhood and not since, and 11 participants continued to have epilepsy, but were controlled on medication. Of these 11 participants, seven were on monotherapy (four on carbamazepine, one on sodium valproate, one on topiramate and one on phenytoin) and four were on two anti-epilepsy drugs (one on phenytoin and carbamazepine, one on phenytoin and topiramate, one on sodium valproate and carbamazepine, and one on carbamazepine and gabapentin).

The non-TSC participant group consisted of adults group-matched for gender, age and IQ. Given the frequency of discrepancies between PIQ and verbal IQ (VIQ) indices in people with TSC (de Vries 2010) and given that the neuropsychological assessments of attention used had relatively low verbal demands, control participants were matched to adults with TSC on PIQ rather than full scale IQ (FSIQ). Of the 25 non-TSC controls originally recruited, two had PIQ below 80, one was unable to have an MRI scan (crucial for the wider project) and four MRI scans were technical failures, so these seven were excluded.

Measures

General intellectual assessment

The Wechsler abbreviated scale of intelligence (WASI), a well validated and widely used measure of global intellectual functioning was administered (Wechsler 1999). The main summary scores from this measure are indices of FSIQ, PIQ and VIQ.

Neuropsychological assessment

The current study was designed as part of a broader study of the neuroanatomical substrates of neuropsychological deficits in children and adults with TSC. The TEA (Robertson et al. 1994) and TEA-Ch were considered for this broader study. Like the TEA-Ch, the TEA includes a cross-modal dual task test (telephone search dual task), but this has been reported to have lower reliability than other TEA tasks. For this reason, the TEA-Ch was chosen to allow for direct comparisons between participants of all ages. By using the same measure across age groups, it was possible to look at attentional abilities in people with TSC from a developmental perspective, albeit at the expense of comparative age appropriate normative data. The TEA-Ch is a standardised pen and paper clinical battery that comprises nine tasks to assess various components of attention, and normative data are available for children between the ages of 6 and 16 years. The authors of the TEA-Ch used a structural equation modelling approach to divide attentional tasks into three main domains: selective attention, sustained attention and attentional control/switching.

Four subtests of the TEA-Ch were used in this study to assess selective attention, sustained attention and dual-tasking

Sky search (selective attention) In this brief timed subtest, participants had to find as many pairs of identical 'spaceship' pairs (targets) among non-identical 'spaceship' pairs (distractors) drawn on a page by putting a circle around the pairs that looked the same. In the second part of the test there were no distractors, which allows for a motor control score to be subtracted from the main task score.

Score! (sustained attention) Participants were asked to count the number of 'score' sounds heard on an audiotape, as if keeping score on a computer game. There were long and variable gaps between 'score' sounds and no other sounds, thus giving little to hold the participant's attention. After every game, the participant was required to report how many sounds he/she had counted.

Sky search dual task (dual tasking) Having previously completed the sky search and score! tasks individually, participants were asked to complete these together in the sky search dual task. At the same time as putting circles around identical pairs of spaceships, they had to count the number of score sounds heard on a tape. Again, score sounds were separated into games, where the participant was required to report the number of scores heard after each game finished. This was therefore a cross-modal dual task. The dual task decrement score was calculated by subtracting the time-per-target (sky search) from the weighted time-per-target on the sky search dual task. The weighted time-per-target was

calculated by dividing the time-per-target by the proportion of counting games correctly reported, so lower scores indicated better performance. Where the resultant dual task decrement score was positive it indicated worse performance on the dual task condition compared to the single task conditions, whereas negative values indicated superior performance on the dual task condition.

Score dual task (dual tasking) This subtest combined the score! task with performing a novel auditory task: at the same time as counting scoring sounds, participants had to listen to a 'news bulletin' containing a single presentation of the name of an animal. Participants were advised to concentrate on counting the scores. After each game, the participant was required to say how many score sounds had been played, as well as what animal was mentioned during the news bulletin. This subtest was a measure of the participant's capacity to allocate attention strategically over time and was a unimodal dual task with relatively low working memory load.

Behaviour rating scales

In order to collect systematic information about attention-related behaviour, the Attention-Deficit Scales for Adults (ADSA) was administered (Triolo and Murphy 1996). This self report measure consists of 54 items that address symptoms of ADHD in adults, divided into nine subscales. Questions relate to everyday activities and experiences, such as "I draw conclusions before knowing all the facts" and "Tasks which need persistence frustrate me." Items are scored on a 5-point Likert scale. This measure has been found to be sensitive to attention-related difficulties in behaviour, but its specificity to ADHD has been questioned (McCann and Roy-Byrne 2004).

Data analysis

All data were analysed using SPSS for Windows version 16. The raw data for each TEA-Ch subscale administered were recorded in line with the manual. As the normative data for the TEA-Ch did not cover the age ranges of the participants in the current study, raw scores were used for analysis. Neuropsychological data were not normally distributed and were therefore analysed using non-parametric statistics. ADSA data were normally distributed and variables were found to have homogeneity of variance. These data were analysed using MANOVA with individual ANOVAs carried out to compare groups for individual subscale scores. To ascertain the level of association between the ability to divide attention between two concurrent tasks and attention-related behaviours in daily life, the correlation between the sky search dual task decrement index from the TEA-Ch and the domain scores from the ADSA was investigated using Spearman's rho.

Results

Participant characteristics

The final sample consisted of 21 adults with TSC and 18 non-TSC controls. The TSC sample included 7 men and 14 women with an average age of 36 years. The non-TSC controls included 7 men and 11 women with an average age of 41 years. There were no group differences in terms of age ($t(35) = -1.407$; $P = 0.168$) or gender ($U = 189$; $P = 1.0$). Table 1 shows the age and WASI scores for participants. Given that we matched participants for non-verbal intelligence, no significant difference was observed in performance IQ ($t(37) = -1.578$; $P = 0.123$). Verbal IQ score on the WASI differed between groups ($t(37) = -2.667$; $P = 0.011$) as did full scale IQ ($t(37) = -2.503$; $P = 0.017$). No participants scored in the borderline IQ or impaired range. The mean verbal and full-scale IQ differences between groups (of <10 points) would not be regarded as significant in a clinical context. No participant (TSC or non-TSC) had received a diagnosis of autism or autism spectrum disorder.

Performance on neuropsychological attention tasks

The results of the TEA-Ch attention tasks are summarised in Table 2. No group differences were observed for the sky search and score! tasks completed separately with the exception of the motor control task (motor time per target) from the sky search task ($U = 112$; $P = 0.045$), where the TSC group displayed slower performance. Statistically significant differences were observed between the groups on the sky search dual task decrement score ($U = 104.5$; $P = 0.027$), with the TSC group showing greater dual task decrements. A box plot showing the range of scores for both groups is displayed in Fig. 1. In terms of performance on the sky search and score! tasks completed concurrently within the dual task condition, a significant group

Table 1 Age and WASI IQ scores for the TSC and non-TSC groups

	TSC group ($n = 21$)		Control group ($n = 18$)	
	Mean (SD)	Range	Mean (SD)	Range
Age	36.31 (12.84)	22–56	41.17 (8.54)	17–55
PIQ	108.67 (12.82)	89–129	114.61 (10.3)	102–137
VIQ	101.48 (12.44)	83–123	111.39 (10.46)	92–136
FSIQ	105.67 (11.79)	86–128	114.72 (10.61)	97–136

Table 2 Performance of Adults with TSC and non-TSC control participants on the TEA-Ch

Task	Variable	TSC group ($n = 21$)		Control group ($n = 18$)		P value
		Mean (SD)	Range	Mean (SD)	Range	
Sky search (SS)	Time per target (s)	4.14 (1.27)	2.3–6.4	3.57 (0.85)	2.3–5.5	0.173
	Motor time per target (s)	1.48 (2.03)	0.6–10	0.85 (0.25)	0.5–1.4	0.045[a]
	Sky search attention score (s)	2.88 (2.05)	−3.7–5.3	2.71 (0.75)	1.6–4.2	0.631
Score!	Proportion of score trials correct (%)	95.24 (12.1)	60–100	99.44 (2.36)	90–100	0.198
SS dual task	Proportion of score trials correct (%)	77.57 (26.17)	25–100	94.06 (16.9)	33–100	0.006[b]
	Time per target (s)	5.42 (2.21)	2.2–9.2	4.65 (2.33)	2.3–11.7	0.208
	Weighted time per target	8.35 (5.65)	3.3–24.8	5.48 (4.06)	2.3–18.2	0.033[a]
	Dual task decrement	4.21 (5.48)	−3–19.9	1.91 (4.25)	−2.3–15.3	0.027[a]
Score! dual task	Proportion of score trials correct (%)	80 (28.28)	10–100	91.67 (15.43)	50–100	0.161
	Proportion of animal trials correct (%)	94.76 (15.69)	30–100	100 (0)	100	0.054
	Proportion of overall games correct (%)	87.38 (20.41)	20–100	95.83 (7.72)	75–100	0.143

[a] $P < 0.05$, [b] $P < 0.01$

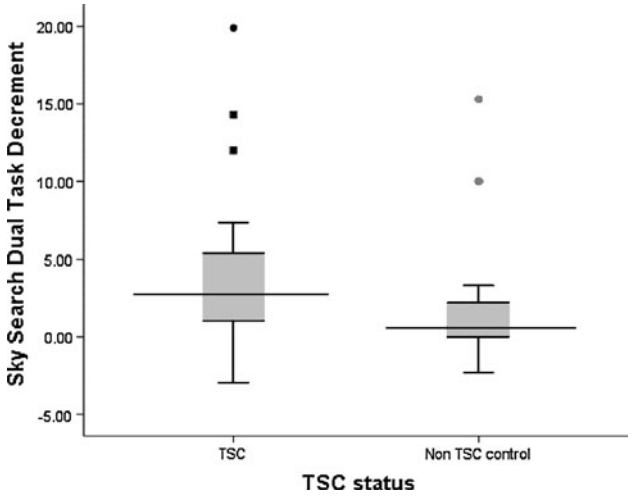

Fig. 1 *Box plot* showing the sky search dual task decrement scores for the TSC ($n = 21$) and non-TSC groups ($n = 18$)

difference was present only for the proportion of score-counting games correct ($U = 102.5$; $P = 0.006$). There was no significant difference in sky search dual task decrement scores between individuals with TSC who had seizures (currently or in the past) compared to those who had never had seizures ($U = 28.0$; $P = 0.248$). No significant group differences were found on the score dual task test ($U = 142.0$; $P = 0.143$).

Attention related behaviours in daily life

The results of the ADSA domain scores are summarised in Table 3. The initial MANOVA suggested that the groups significantly differed in terms of scores on one or more of the ADSA subscales (Wilk's $\Lambda = 0.335$; $F(10, 25) = 4.972, P = 0.001, \eta^2 = 0.665$) indicating a large effect size. On further analysis, statistically significant differences were demonstrated in the total score ($F(1, 34) = 8.839$,

Table 3 Attention-Deficit Scales for Adults (ADSA) subscale T scores for the TSC and non-TSC groups

Subscale	TSC group ($n = 18$)		Control group ($n = 18$)		ANOVA	P value	η^2 [e]
	Mean (SD)	Range	Mean (SD)	Range			
Total	53.61 (11.31)	35–75	43.11 (9.83)	30–62	$F(1, 34) = 8.84$	0.005[c]	0.206
Attention–focus/concentration	54.44 (11.0)	40–77	42.5 (8.9)	30–60	$F(1, 34) = 12.81$	0.001[d]	0.274
Interpersonal	47.44 (10.56)	30–70	47.44 (11.74)	30–70	$F(1, 34) = .00$	1.00	0.000
Behaviour-disorganised activity	51.67 (9.49)	32–71	43.33 (10.56)	30–71	$F(1, 34) = 6.2$	0.018[a]	0.154
Coordination	54.72 (14.29)	39–90	50.44 (10.15)	39–65	$F(1, 34) = 1.07$	0.308	0.031
Academic theme	58.33 (14.43)	30–84	46.22 (7.81)	38–66	$F(1, 34) = 9.8$	0.004[c]	0.224
Emotive	56.83 (14.14)	30–78	43.22 (9.53)	30–61	$F(1, 34) = 11.46$	0.002[c]	0.252
Consistency/long-term	51.22 (12.5)	34–79	46.61 (11.04)	30–67	$F(1, 34) = 1.38$	0.249	0.039
Childhood	52.94 (16.43)	30–86	50.61 (12.35)	30–72	$F(1, 34) = .23$	0.633	0.007
Negative-social	48.11 (10.74)	32–86	47.5 (9.74)	30–62	$F(1, 34) = .03$	0.859	0.001

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.005$, [d] $P < 0.001$, [e] Partial Eta Squared, measure of effect size. Effect sizes above 0.14 are considered large

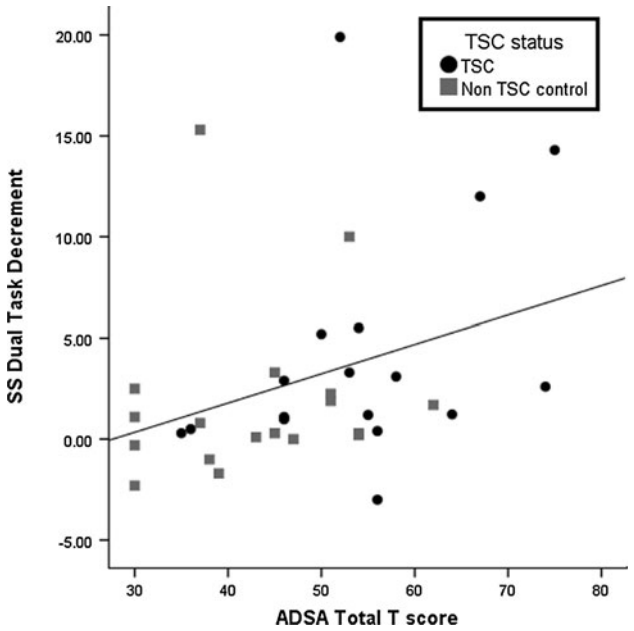

Fig. 2 *Scatter plot* demonstrating the correlation between the sky search dual task decrement and the ADSA total *T* score for the TSC and non-TSC group combined ($\rho = 0.373$, $P = 0.027$, $n = 35$)

$P = 0.005$; $\eta^2 = 0.206$) and in four domains: attention/concentration ($F(1, 34) = 12.814$, $P = 0.001$; $\eta^2 = 0.274$), behaviour/disorganization ($F(1, 34) = 6.203$, $P = 0.018$; $\eta^2 = 0.154$), academic ($F(1, 34) = 9.798$, $P = 0.004$; $\eta^2 = 0.224$) and emotive ($F(1, 34) = 11.463$, $P = 0.002$; $\eta^2 = 0.252$) with all effect sizes in the large range (Cohen 1988). Those with a history of seizures and those without did not differ in terms of ADSA total scores ($U = 19.0$; $P = 0.110$) or any subscale score.

Significant correlations were observed between the sky search dual task decrement score and the ADSA total *T* score ($\rho = 0.373$, $P = 0.027$; see Fig. 2) in addition to four subscale scores: attention-focus/concentration ($\rho = 0.365$, $P = 0.031$), behaviour-disorganised activity ($\rho = 0.401$, $P = 0.017$), academic theme ($\rho = 0.424$, $P = 0.011$) and emotive ($\rho = 0.475$, $P = 0.004$).

Discussion

This study investigated neuropsychological attention skills in normally intelligent adults with TSC. Following reports of dual task deficits in children with TSC (de Vries et al. 2009), we were particularly interested in the ability of adults with TSC to carry out two tasks simultaneously. TSC and non-TSC participants completed four subtests from the TEA-Ch, including a cross-modal dual task, which involves concurrent performance of a visual search task and an auditory sustained attention task. Our results indicated that normally intelligent adults with TSC have significant neuropsychological attention difficulty when allocating attention across modalities compared to control participants. No significant group differences were found in the sustained or selective attention tasks completed alone. Significant correlations were observed between performance on the cross-modal dual task subtest of the TEA-Ch and the ADSA self-report measure of attention-related behaviour difficulties in adults, suggesting that these attentional deficits impact on daily life. No differences were found in cross-modal dual tasking or the total ADSA score between individuals with TSC who had a history of seizures and those who did not.

The results from the current study corroborate and extend previous findings of reduced attentional abilities in individuals with TSC. Similar to the performance of children with TSC on the TEA-Ch (de Vries et al. 2009), adults with TSC have particular difficulty in dividing attentional resources between two tasks: one in the visual modality (a visual search task with distractors) and an auditory sustained attention task (counting target sounds with variable inter-stimulus intervals). They were able to do the visual search component task, but showed significantly reduced performance on the auditory sustained attention component, despite no such deficit being evident when the same task was completed alone. We therefore suggest that with the extra demand required to allocate attentional resources, auditory sustained attention was disproportionately affected with relative preservation of visual selective attention.

In contrast to the results of the study of attention in children with TSC, the current sample of adults did not have impairments on other tests of selective or sustained attention, nor was any impairment found on the unimodal dual task subtest. It is interesting to note that a significant group difference was found on the motor control component (motor time per target) of the visual search task, suggesting that adults with TSC are slower to provide the type of motor response necessary to complete the sky search task. This group difference was not large enough to impact on overall performance on the visual search task, and it is unlikely to be a sufficient explanation for the dual task decrement observed, as performance on the visual search task completed individually is taken into consideration when calculating the decrement score. The score dual task is a test of unimodal divided attention with both tasks in the auditory modality. This test is likely to place lower demands on cognitive resources. As such, the observation that adults with TSC are selectively impaired on a cross-modal dual task test may relate to the level of demand required to complete the task. Further research utilising additional unimodal and cross-modal dual task paradigms is required to clarify this prediction.

These findings suggest that deficits in dual task performance are a consistent feature of the neuropsychological

phenotype of TSC across the lifespan. De Vries and Watson proposed a 'conditional pattern of attentional development', in which performance on the cross-modal dual task relies on unimpaired skills in the component tasks (i.e. visual search and auditory sustained attention) as well as an extra executive component required to divide attention (de Vries and Watson 2008). The authors found evidence to support this hypothesis in 90% of their sample, and concluded that unimpaired performance on the sky search dual task was reliant on sufficient development of skills thought to mature at an earlier developmental stage. The findings of the current study suggest that adults with TSC have achieved functional skills such as sustained auditory attention but are impaired on higher level attentional skills theorised to mature later. More complex skills such as dual task performance may remain impaired in many people with TSC, even in adulthood and in the context of normal intellectual ability. Longitudinal research is needed to assess the developmental trajectory of attentional skills of people with TSC in more detail.

The observation that the presence or absence of epilepsy (including current seizures and anti-epilepsy medication) did not influence dual task decrement or ADSA scores suggests that neuropsychological attention deficits and related attention deficit behaviours in daily life in TSC are not determined by seizures.

Several methodological limitations are worthy of note. The advantage of using the TEA-Ch was that the cross-modal dual subtest had higher reliability compared to the equivalent TEA task, and also that it allowed for direct comparison with previous attention research on children with TSC. A disadvantage of the TEA-Ch was the possibility of ceiling effects. Interestingly, results showed ceiling effects only on one task (auditory sustained attention) and this was true only for non-TSC participants. If anything, the current results may therefore underestimate the level of attentional impairment in adults with TSC.

In summary, adults with TSC with normal global intellectual abilities have specific difficulties with attentional skills when carrying out a cross-modal dual task. Dual task performance was correlated with self-reported difficulties with attention-related behaviours in daily life. We suggest that dual task deficits may be a common and consistent feature of the neuropsychological phenotype of TSC.

Acknowledgment The authors thank Dr. Alia Ul-Hassan for comments on an earlier draft of the paper.

Conflict of interest None

Funding The study was funded by a Tuberous Sclerosis Alliance Innovative Science Award to PdV. Additional support was provided by the Cambridgeshire and Peterborough NHS Foundation Trust and NHS Flexibility and Sustainability Funding.

References

Cohen J (1988) Statistical power analysis for the behavioural sciences, 2nd edn. Lawrence Erlbaum Associates, Hillsdale

Crino PB, Nathanson KL, Henske EP (2006) The tuberous sclerosis complex. N Engl J Med 355:1345–1356

Curatolo P, Bombardieri R, Jozwiak S (2008) Tuberous sclerosis. Lancet 372:657–668

de Vries PJ (2010) Neurodevelopmental, psychiatric and cognitive aspects of tuberous sclerosis complex. In: Kwiatkowski DJ, Whittemore VH, Thiele EA (eds) Tuberous sclerosis complex: genes, clinical features, and therapeutics. Wiley-VCH, Weinheim, pp 229–266

de Vries PJ, Howe CJ (2007) The tuberous sclerosis complex proteins: a GRIPP on cognition and neurodevelopment. Trends Mol Med 13:319–326

de Vries PJ, Hunt A, Bolton PF (2007) The psychopathologies of children and adolescents with tuberous sclerosis complex (TSC): a postal survey of UK families. Eur Child Adolesc Psychiatry 16:16–24

de Vries PJ, Prather PA (2007) The tuberous sclerosis complex. N Engl J Med 356:92–94

de Vries PJ, Watson P (2008) Attention deficits in tuberous sclerosis complex (TSC): rethinking the pathways to end state. J Intellect Disabil Res 52:848–857

de Vries PJ, Humphrey A, McCartney D, Prather P, Bolton P, Hunt A (2005) Consensus clinical guidelines for the assessment of cognitive and behavioural problems in tuberous sclerosis. Eur Child Adolesc Psychiatry 14:183–190

de Vries PJ, Gardiner J, Bolton PF (2009) Neuropsychological attention deficits in tuberous sclerosis complex (TSC). Am J Med Genet 149A:387–395

Ehninger D, Silva AJ (2011) Increased levels of anxiety-related behaviors in a Tsc2 dominant negative transgenic mouse model of tuberous sclerosis. Behav Genet. doi:10.1007/s10519-010-9398-1 (online early BEGE)

Ehninger D, Han S, Shilyansky C, Zhou Y, Li W, Kwiatkowski DJ, Ramesh, Silva AJ (2008) Reversal of learning deficits in a *Tsc2*$^{+/-}$mouse model of tuberous sclerosis. Nat Med 14:843–848

Gillberg JC, Gillberg C, Ahlsén G (1993) Autistic behaviour and attention deficits in tuberous sclerosis: a population based study. Dev Med Child Neurol 36:50–56

Goorden SM, van Woerden GM, van der Weerd L, Cheadle JP, Elgersma Y (2007) Cognitive deficits in Tsc1 ± mice in the absence of cerebral lesions and seizures. Ann Neurol 62: 648–655

Harrison JE, O'Callaghan FJ, Hancock E, Osborne JP, Bolton PF (1999) Cognitive deficits in normally intelligent patients with tuberous sclerosis. Am J Med Genet 88:642–646

Jansen FE, Braams O, Vincken KL, Algra A, Anbeek P, Jennejens-Schinkel A, Halley D, Zonnenberg BA, van den Ouweland A, van Huffelen AC, van Nieuwenhuizen O, Nellist M (2008) Overlapping neurologic and cognitive phenotypes in patients with TSC1 or TSC2 mutations. Neurology 70:908–915

Joinson C, O'Callaghan FJ, Osborne JP, Martyn C, Harris T, Bolton PF (2003) Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med 33:335–344

Kwiatkowski DJ (2010) Genetics of tuberous sclerosis complex. In: Kwiatkowski DJ, Whittemore VH, Thiele EA (eds) Tuberous sclerosis complex: genes, clinical features, and therapeutics. Wiley-VCH, Weinheim, pp 29–60

Manly T, Robertson IH, Anderson V, Nimmo-Smith I (1999) Test of Everyday Attention for Children (TEA-Ch) manual. Thames Valley Test Company, Suffolk

Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH (2001) The differential assessment of children's attention: the test of everyday attention for children (TEA-Ch), normative sample and ADHD performance. J Child Psychol Psychiatry 42:1065–1081

McCann BS, Roy-Byrne P (2004) Screening and diagnostic utility of self-report attention deficit hyperactivity disorder scales in adults. Compr Psychiatry 45:175–183

Osborne JP, Fryer A, Webb D (1991) Epidemiology of tuberous sclerosis. Ann N Y Acad Sci 615:125–127

Povey S, Burley MW, Attwood J, Benham F, Hunt D, Jeremiah SJ, Franklin D, Gillett G, Malas S, Robson EB, Tippett P, Edqards JH, Kwiatkowski DJ, Super M, Mueller R, Fryer A, Clarke A, Webb D, Osborne J (1994) Two loci for tuberous sclerosis: one on 9q34 and one on 16p13. Ann Hum Genet 58:107–127

Prather PA, de Vries PJ (2004) Behavioral and cognitive aspects of tuberous sclerosis complex. J Child Neurol 19:666–674

Prather PA, Thiele EA, de Vries PJ (2006) Neuropsychological profiling in tuberous sclerosis complex (TSC): implications for neurobiological and clinical interventions. J Intellect Disabil Res 50:788

Ridler K, Suckling J, Higgins NJ, de Vries PJ, Stephenson CME, Bolton PF (2007) Neuroanatomical correlates of memory deficits in tuberous sclerosis complex. Cereb Cortex 17:261–271

Roach ES, Gomez M, Northrup H (1998) Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol 13:624–628

Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I (1994) The test of everyday attention: manual. Thames Valley Test Company, Suffolk

Serfontein J, Nisbet RER, Howe CJ, de Vries PJ (in press) Conservation of structural and functional elements of TSC1 and TSC2: a bioinformatic comparison across animal models. Behav Genet. doi:10.1007/s10519-010-9440-3

Serfontein J, Nisbet RER, Howe CJ, de Vries PJ (2010) Evolution of the TSC1/TSC2-TOR signaling pathway. Sci Signal 3(128):ra49

Triolo SJ, Murphy KR (1996) Attention-Deficit Scales for Adults (ADSA): manual for scoring and interpretation. Brunner/Mazel Publishers, New York

Waltereit R, Japs B, Schneider M, de Vries PJ, Bartsch D (2011) Epilepsy and *Tsc2* haploinsufficiency lead to autistic-like social deficit behaviors in rats. Behav Genet. doi:10.1007/s10519-101-9399-0 (online early BEGE)

Waltereit R, Welzi H, Dichigans J, Lipp HP, Schmidt WJ, Weller M (2006) Enhanced episodic-like memory and kindling epilepsy in a rat model of tuberous sclerosis. J Neurochem 96:407–413

Wechsler D (1999) Wechsler Abbreviated Scale of Intelligence (WASI). Harcourt Assessment, San Antonio