Received: 19 January 2024 | Revised: 5 April 2024 | Accepted: 27 April 2024

DOI: 10.1002/ajmg.a.63653

ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Neuropsychological functioning of adults with *PTEN* hamartoma tumor syndrome

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Funding information
Radboud Oncologie Fonds

Abstract

PTEN hamartoma tumor syndrome (PHTS) might be associated with a distinct cognitive and psychological profile. However, previous studies are limited, predominantly based on small and pediatric cohorts, likely affected by selection bias, and show a broad range of findings. We aimed to characterize the neuropsychological functioning of adults with PHTS. A total of 40 participants, with intellectual disability as exclusion criterium, completed an extensive clinical neuropsychological assessment including cognitive tasks, questionnaires, and a clinical diagnostic interview. The cognitive tasks and questionnaire data were categorized as below and above average based on 1.5 *SD*. About 80% of participants showed an average level of intelligence. In addition, 30% and 24% of participants scored below average on immediate memory recall and speed of information processing, respectively. Furthermore, about 25% reported above average scores on the majority of the questionnaires, indicating psychological distress, signs of alexithymia, and cognitive complaints. Personality of participants was characterized by inflexibility, social withdrawal, and difficulties in recognizing and describing their own emotions. Adults with PHTS demonstrate a heterogeneous yet distinct neuropsychological profile that is characterized by slower information processing, psychological problems, and specific personality traits. These findings provide directions on how to optimize the care and daily lives of adults with PHTS.

KEYWORDS
behavior, cognition, emotions, personality assessment, psychopathology, PTEN hamartoma tumor syndrome

1 | INTRODUCTION

PTEN hamartoma tumor syndrome (PHTS, comprising Bannayan-Riley Ruvalcaba Syndrome and Cowden Syndrome) is a rare genetic syndrome caused by pathogenic germline variants in the *PTEN* gene. The clinical spectrum of PHTS is diverse and includes macrocephaly, autism, developmental delay, benign tissue overgrowth (e.g., Lhermitte-Duclos disease, colorectal hamartomas, and thyroid nodules), and an increased risk for cancer of the breast, endometrium, thyroid, colorectum, kidney, and skin (Dutch Society of Clinical

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Genetics (VKGN), 2015; Hendricks et al., 2023; Pilarski, 2019). Initially, children with PHTS are often identified because of autism and/or developmental delay, whereas adults with PHTS are often identified because of early-onset cancer. Due to the increased lifetime risks of cancer, adults with PHTS are advised to participate in cancer surveillance programs from age 18 aimed at enabling early detection and treatment of cancer (Dutch Society of Clinical Genetics (VKGN), 2015; Tischkowitz et al., 2020).

During surveillance visits at our unique PHTS expertise center, we noticed a remarkably high number of adults with PHTS exhibiting specific behavior interfering with clinician-patient interaction. In this (unpublished) pilot study, the behavior of adults with PHTS was scored by their treating physician directly after the outpatient clinic visit and compared to individuals with other cancer predisposition syndromes. Based on the results, adults with PHTS more often showed a difficult physician–patient relationship (e.g., tense contact, difficulty in providing information to patients, and less patient compliance to commitments), and problematic behavioral characteristics related to emotional and social functioning, verbal and motor functioning, and executive functioning. According to literature, these interaction problems could have a negative impact on patients' understanding of the purpose, expectations, and involvement of care (e.g., compliance with cancer surveillance participation) and thereby hamper the delivery of high-quality health care (Ha & Longnecker, 2010).

Problems in the clinician–patient interaction can be caused by various factors, including cognitive and psychological difficulties that patients may face. For example, cognitive weaknesses such as memory problems or difficulties in social cognition (i.e., the ability to attribute feelings, ideas, and intentions to themselves and to others) can lead to information being not properly absorbed, comprehended, or expressed (MacDonald, 2017). Also, psychological problems such as anxiety, depression, frustration, and stress can, for example, coincide with distraction, resistance, or passivity and lead to ineffective interaction (Kolb et al., 2019). Therefore, knowledge of an individual's cognitive and psychological functioning is essential for a better understanding of the experienced problems in clinician–patient interaction.

Regarding cognitive functioning, a broad range of levels of intellectual functioning has been observed in individuals with PHTS varying from intellectual disability to normal intelligence levels (Busch et al., 2013; Hansen-Kiss et al., 2017; Plamper et al., 2020; Shiohama et al., 2020). Busch et al. (2013) studied cognition in a predominantly adult PHTS cohort using a formal neuropsychological test battery, showing an average level of intelligence that varied widely from exceptionally low to exceptionally high as well as problems in executive, motor, and memory function. Another study observed deficits in motor functioning and altered social cognition in adults with PHTS, as reflected by difficulties in facial emotion recognition and in mentalizing and social contexts understanding (Desjardins et al., 2023).

Psychological functioning in PHTS has primarily been described in terms of diagnostic classifications of psychiatric disorders, of which autism spectrum disorder (ASD) is the most commonly reported classification, and has an estimated prevalence of 25% (Cummings et al., 2022). Previous studies have shown reduced adaptive behavioral functioning and more sensory abnormalities in children with PHTS and ASD when compared to non-PHTS children with ASD (Busch et al., 2019; Frazier et al., 2015). In contrast, lower clinical ratings of autism symptoms severity were found in children with PHTS and ASD. In adults with PHTS, symptoms of anxiety, bipolar disorder, and obsessive-compulsive symptoms have been observed as well as adult onset movement disorder and psychosis in two of six families (Balci et al., 2018).

To date, studies on the cognitive and psychological functioning of individuals with PHTS are scarce, show a broad range of findings, are predominantly based on non-formal assessment and small cohorts mainly comprising children, and are likely affected by selection bias, which emphasizes the need for further investigation. To improve our understanding of the PHTS phenotype and provide directions on how to optimize the care and daily lives of individuals with PHTS, the aim of this study was to characterize the cognitive and psychological functioning, collectively termed neuropsychological functioning, of adults with PHTS.

2 | METHODS

2.1 | Setting

This study included 40 adults with PHTS (aged ≥18 years) with surveillance and/or genetic testing at the PHTS expertise center of the Radboud University Medical Centre (Radboudumc). Adults with (clinical signs of) intellectual disability or pathogenic variants in genes other than *PTEN* were not considered for inclusion. All participants had a confirmed (likely) pathogenic *PTEN* variant, except for one individual in whom *PTEN* testing had not been performed but who had a first-degree relative with confirmed PHTS and fulfilled the clinical PHTS diagnosis (National Comprehensive Cancer Network (NCCN), 2022). The distribution of PHTS index patients (i.e., the first person in a family diagnosed with PHTS) and non-index patients was equal. Ethical approval was obtained from the Institutional Review Board of the Radboudumc (2020-7068), and all participants provided written informed consent.

2.2 | Materials

All participants completed a clinical neuropsychological assessment including measures of cognitive and psychological functioning, assessed by various cognitive tasks, questionnaires, and a clinical diagnostic interview (Figure S1). Cognitive functioning included measures of intelligence, attention, executive functioning, memory, and social cognition. Measures of psychological functioning included personality, psychopathology, and emotional-behavioral functioning. Demographic (e.g., occupation, education) and clinical information (e.g., history of psychological classifications, cancer history) of the cohort were asked

during the interview and cognitive tasks and supplemented with medical record data. During and directly after each assessment, systematic cognitive and behavioral observations of the participants were notated by the psychologist with a checklist. This checklist was compiled and adapted based on existing validated observation forms, with emphasis on different features of behavioral, attentional, executive, and social functioning (e.g., quality of eye contact and attention span) (Deelman et al., 2006; McConaughy & Achenbach, 2004; Persoon et al., 2012).

2.2.1 | Cognitive tasks

The cognitive tasks took ~3–4 h and were conducted by a psychologist (CO) at the participant's home, the Radboudumc, or the Vincent van Gogh Institute depending on the participant's preference. Intelligence was measured with the Wechsler Adult Intelligence Scale-IV-NL (WAIS-IV-NL) (Wechsler, 2012). The interference score of the Stroop Color Word Test (time required on card 3 divided by time required on card 2) and the measure of cognitive flexibility from the Trail Making Test (TMT; time required on part B divided by time required on part A) were used as a measure for attention (Hammes, 1971; Reitan, 1958). Measures of executive functioning included the intra/extradimensional shifting task (IED, measuring visual discrimination, attentional set formation maintenance, shifting, and flexibility) and Stockings of Cambridge (SOC, measuring spatial planning and problem-solving strategies) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, 2006). Memory was measured by the Auditory Verbal Learning Task (AVLT) (Bishop et al., 1990). Social cognition was assessed by the Dutch Theory of Mind test Revised (ToM test-R) and the emotion recognition task (ERT) (Montagne et al., 2007; Steerneman, 2009). The ToM test-R was used to determine the participants' (cognitive) ability to attribute feelings, ideas, and intentions to themselves and others. A maximum score on this task was considered average, as norms are based on individuals aged 0–12 years.

2.2.2 | Questionnaires

In total, four questionnaires were sent to the participants. The Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) was used to measure views of an adult's executive functions in everyday life (Scholte & Noens, 2011). The Toronto Alexithymia Scale (TAS-20) was used to assess alexithymia, that is, difficulty identifying and describing one's emotions (Bagby et al., 1994). Types of strategies participants use to regulate their own emotions were measured with the Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen (FEEL-E) questionnaire (Grob et al., 2015). The Symptom Checklist-90-R (SCL-90) was used as a self-report questionnaire to assess various psychological and physical problems, for example, anxiety, depression, and somatic complaints (Arrindell & Ettema, 1986).

2.2.3 | Diagnostic interview

The Clinical Diagnostic Interview, a systematic interview assessed by video calling, was conducted by a psychologist (CO) and took ~2 h. The Dutch version of the Shedler-Western Assessment Procedure (SWAP-200-NL) was applied to process the information retrieved during the interview (Lie Sam Foek-Rambelje et al., 2020; Shedler & Westen, 2007). The trait dimension factors of the SWAP-200-NL were used to assess personality traits (Shedler, 2009).

2.3 | Data processing and statistical analyses

Descriptive statistics are reported using appropriate measures depending on data distribution. All measures were scored according to the corresponding manual by using age-corrected, and when available, education-corrected, norms. Data from the cognitive tasks and questionnaires were translated into *z*-scores and categorized as below average, average, and above average using 1.5 standard deviation (*SD*) as cutoff point to obtain a clinical impression of the performances. Chi-squared tests were performed to assess whether the proportion of participants scoring below or above average differed significantly from proportions that would be expected in the norm group based on 1.5 *SD* (7% below average, 86% average, and 7% above average). Data from the SWAP-200-NL were translated into *T*-scores and categorized as average (*T*-score of 0–55), showing clinically significant features of a specific personality trait (*T*-score of ≥55), and showing a clinically significant personality trait (*T*-score of ≥60). Since norms of the SWAP-200-NL are based on a clinical sample of individuals with DSM-IV Axis II diagnoses rather than healthy individuals, participants' *T*-scores were assessed in a descriptive manner and not statistically compared to norm scores. As a secondary analysis, Mann–Whitney *U* tests and Chi-squared tests were performed to assess whether index patients differed from non-index patients on the neuropsychological measures and baseline characteristics, respectively. Both statistically significant differences ($p \leq 0.05$) and marginally statistically significant differences ($p > 0.05$ and $p < 0.10$) were reported when considering the small cohort size in absolute terms and the clinical relevance of results nearly reaching statistical significance. Statistical analyses were performed in SPSS and R Studio.

3 | RESULTS

3.1 | Study participants

Of all 40 participants, one was excluded from all analyses due to a diagnosis of Parkinson's disease shortly after study completion (which has not been described at high frequencies within PHTS cohorts), as this could influence neuropsychological functioning. One additional participant was excluded from the cognitive task results due to severe retinitis pigmentosa, which interfered with the standard administration of cognitive tasks. Another participant

TABLE 1 Baseline characteristics of the cohort.

	Cohort ($N = 39$)
General	
Female gender	23/39 (59%)
Age, mean (range)	
At completion of first measurement	37 (18–66)
At completion of last measurement	38 (18–66)
Age at PHTS diagnosis, mean (range)	35 (1–63)
Right-hand preference	31/38 (82%)
Current employment status	
Employed	24/39 (62%)
Non-employed	7/39 (18%)
Student	8/39 (21%)
Highest educational level[a], mean (range)	5 (4–7)
Living situation	
Alone	5/39 (13%)
With partner	24/39 (62%)
With parent(s)	10/39 (26%)
Worrying a lot (self-reported)	23/37 (62%)
Autistic traits (self-reported)	19/35 (54%)
Former or current smoker	2/38 (6%)
Alcohol drinker	29/37 (78%)
Former or current drug user	1/38 (3%)
Medical[b]	
Macrocephaly	29/35 (83%)
Hearing impairment[c]	1/38 (3%)
Visual impairment[d]	22/35 (63%)
Brain MRI findings	7/39 (18%)
Lhermitte-Duclos disease	3
Chiari malformation	1
Meningioma	1
Other benign abnormalities	2
Epilepsy	2/39 (5%)
Stroke	1/39 (3%)
Motor or intellectual delay	3/39 (8%)
Motor skill or language problems	4/39 (10%)
Psychological/psychiatric disorder	18/39 (46%)
Burn-out[e]	7
Trauma- and stress-related disorders[f]	7
Depression disorder	5
Anxiety disorder	4
Personality disorder	3
Autism spectrum disorder	2
Other[g]	3
Psychological/psychiatric treatment	24/39 (62%)
Outpatient treatment	20
Inpatient treatment	1
Coaching	1
Mental health practitioner	2
Medication[h]	19/38 (50%)
Cancer history[i]	11/38 (29%)
Breast cancer	5
Endometrial cancer	0
Thyroid cancer	2
Colorectal cancer	1
Renal cancer	0
Melanoma	2
Other[j]	1

Note: Data are presented as *n*/*N* (%) unless indicated differently.
[a]Coded according to the Dutch educational system using seven categories ranging from 1 (< primary school) to 7 (academic degree): (1) 1–5 years ($n = 0$); (2) 6 years ($n = 0$); (3) 7–8 years ($n = 0$); (4) 7–9 years ($n = 4$); (5) 7–10 years ($n = 19$); (6) 7–16 years ($n = 9$); (7) 17–20 years ($n = 7$) (Bouma et al., 2012). This system is comparable to the UNESCO International Standard Classification of Education (UNESCO Institute for Statistics, 2012).
[b]Medical information prior to participation in this study.
[c]Hearing of high tones impaired ($n = 1$).
[d]Near- or far-sightedness ($n = 19$), amblyopia ($n = 1$), and retinitis pigmentosa ($n = 2$).
[e]A syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed (World Health Organization, 2019).
[f]Disorders in which exposure to a traumatic or stressful event is listed explicitly as a diagnostic criterion, which include reactive attachment disorder, disinhibited social engagement disorder, posttraumatic stress disorder (PTSD), acute stress disorder, adjustment disorders, and prolonged grief disorder (American Psychiatric Association, 2013).
[g]Ambivalent attachment disorder ($n = 1$), attention-deficit hyperactivity disorder ($n = 1$), and somatisation disorder ($n = 1$).
[h]Thyroid medicines ($n = 6$), gastrointestinal medication ($n = 5$), anti-depressants ($n = 4$), anti-histamines ($n = 4$), anticoagulation medication ($n = 3$), AD(H)D medication ($n = 1$), anti-epileptics ($n = 1$), anti-fungal medicines ($n = 1$), anti-hypertensive medication ($n = 1$), benzodiapines ($n = 1$), cancer medicines ($n = 1$), opioids ($n = 1$), and other ($n = 10$).
[i]Cancer treatment consisted of a combination of surgery and chemotherapy ($n = 5$), combination of surgery and radiation therapy ($n = 2$), and surgery only ($n = 3$).
[j]Testicular cancer ($n = 1$).

withdrew from the study after completing the interview and questionnaires. Consequently, 37 participants were included in the cognitive measures and 39 participants in the diagnostic interview and questionnaire data. Of all 39 participants, 23 (59%) were female (Table 1). The mean age at study completion was 38 years ($SD = 12.7$, range = 18–66). Regarding psychological history, 18 (46%) participants had been classified with a psychological disorder prior to study participation, including trauma- and stress-related disorders (18%), burn-out (18%), depression (13%), anxiety (10%), personality disorder (8%), and ASD (5%). Furthermore, 24 (62%) participants received psychological or psychiatric treatment. Twenty-three participants (62%) reported worrying a lot and 19 (54%) recognized autistic traits in themselves. Twenty participants (51%) were index patients, and no relevant differences in baseline characteristics were observed between both groups.

3.2 | Cognitive functioning

3.2.1 | Cognitive tasks

About 80% of participants showed an average level of intelligence, which overall varied from below average to above average ($M = 94.41$, range = 71–112) based on the classification of Guilmette et al. (Table 2 and Figure 1). Furthermore, 30% and 24% scored below average on the immediate memory recall of the AVLT and the speed of information processing scale of the WAIS-IV, respectively, indicating lower performance when compared to norm scores ($p < 0.05$ and $p < 0.10$, respectively). The proportion of participants scoring below average was <20% on the remaining tasks, and indicated no differences when compared to norm scores ($p > 0.10$). Higher performance was also observed, as shown by 62% and 43% of participants scoring above average on the Stroop-test interference score ($p < 0.001$) and the ToM-R test ($p < 0.001$), of which the latter could be explained by the fact that norms are based on children aged 0–12 years. To get a better understanding of the high Stroop-test scores, the performance on the underlying subtests (cards I–III) was examined, resulting in *z*-scores that indicated a low average performance on card I ($M = -1.01$ $SD = 1.28$) and II ($M = -0.66$, $SD = 1.23$), with average performance on card III ($M = 0.03$, $SD = 0.96$).

3.3 | Psychological functioning

3.3.1 | Questionnaires

Of all 39 participants, 26% reported above-average scores on the general psychoneuroticism scale, followed by 33% on the sleeping difficulties subscale and 36% on the cognitive performance deficits subscale of the SCL-90 (Table 3 and Figure 2). These proportions were all significantly higher when compared to norm scores ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively). Furthermore, 23% of participants reported above average scores on the SCL-90 anxiety and depression symptoms scale, alexithymia symptoms on the TAS-20, and experienced executive problems on the BRIEF-A, indicating higher scores when compared to norm scores (all $p < 0.10$). The proportion of participants scoring above average was <21% for the other measures, and indicated no differences when compared to norm scores ($p > 0.10$).

3.3.2 | Diagnostic interview

The most commonly observed personality traits included psychological health (100%), obsessionality (33%), dissociation (26%), and

TABLE 2 Cognitive task scores in adults with PHTS, compared to norm scores (presented as *z*-scores).

Measure	*N*	Mean (SD)	Min	Max	Median	% below average, <−1.5 SD (expected % in norm group)	% average, −1.5 to 1.5 SD (expected % in norm group)	% above average, >1.5 SD (expected % in norm group)
Intelligence								
WAIS-IV-NL FIQ	37	−0.37 (0.98)	−1.93	1.73	−0.47	16.2 (7)	81.1 (86)	2.7 (7)
WAIS-IV-NL VCI	37	−0.21 (0.93)	−2.40	1.33	−0.33	5.4 (7)	94.6 (86)	0.0 (7)
WAIS-IV-NL PRI	37	−0.31 (1.06)	−2.00	1.40	−0.40	18.9 (7)	81.1 (86)	0.0 (7)
WAIS-IV-NL WMI	37	0.01 (1.10)	−2.13	1.93	0.20	10.8 (7)	75.7 (86)	13.5 (7)
WAIS-IV-NL PSI	37	−0.71 (0.87)	−2.47	2.07	−0.60	24.3 (7)*	73.0 (86)	2.7 (7)
Attention/executive functioning								
TMT	37	−0.09 (1.01)	−2.70	3.13	−0.11	10.8 (7)	86.5 (86)	2.7 (7)
Stroop	37	1.70 (0.76)	−0.08	3.86	1.80	0.0 (7)	37.8 (86)	**62.2 (7)****
CANTAB IED—total errors	37	−0.28 (0.85)	−2.33	0.77	0.15	5.4 (7)	94.6 (86)	0.0 (7)
CANTAB SOC—total problems solved	36	0.09 (0.97)	−1.75	2.33	0.02	8.3 (7)	86.1 (86)	5.6 (7)
Memory								
AVLT—immediate recall	37	−0.77 (0.91)	−2.23	0.74	−0.85	**29.7 (7)****	70.3 (86)	0.0 (7)
AVLT—delayed recall	37	−0.55 (0.99)	−2.91	1.66	−0.56	18.9 (7)	78.4 (86)	2.7 (7)
Social cognition								
ERT	36	−0.90 (0.70)	−2.60	0.52	−0.84	19.4 (7)	80.6 (86)	0.0 (7)
ToM-R	37	0.57 (0.97)	−2.00	1.50	0.50	2.7 (7)	54.1 (86)	**43.2 (7)****

Note: A higher mean indicates a better performance. *<0.10, **<0.05, ***<0.01, and ****<0.001 based on Chi-squared tests.
Abbreviations: AVLT, auditory verbal learning task; CANTAB, Cambridge Neuropsychological Test Automated Battery; ERT, emotion recognition task; FIQ, full-scale IQ; IED, intra/extradimensional shifting task; PHTS, PTEN hamartoma tumor syndrome; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; SOC, stockings of Cambridge; TMT, trail making test; ToM-R, Dutch Theory of Mind test revised; VCI, verbal comprehension index; WAIS-IV-NL, Wechsler Adult Intelligence Scale-IV-NL; WMI, working memory index.

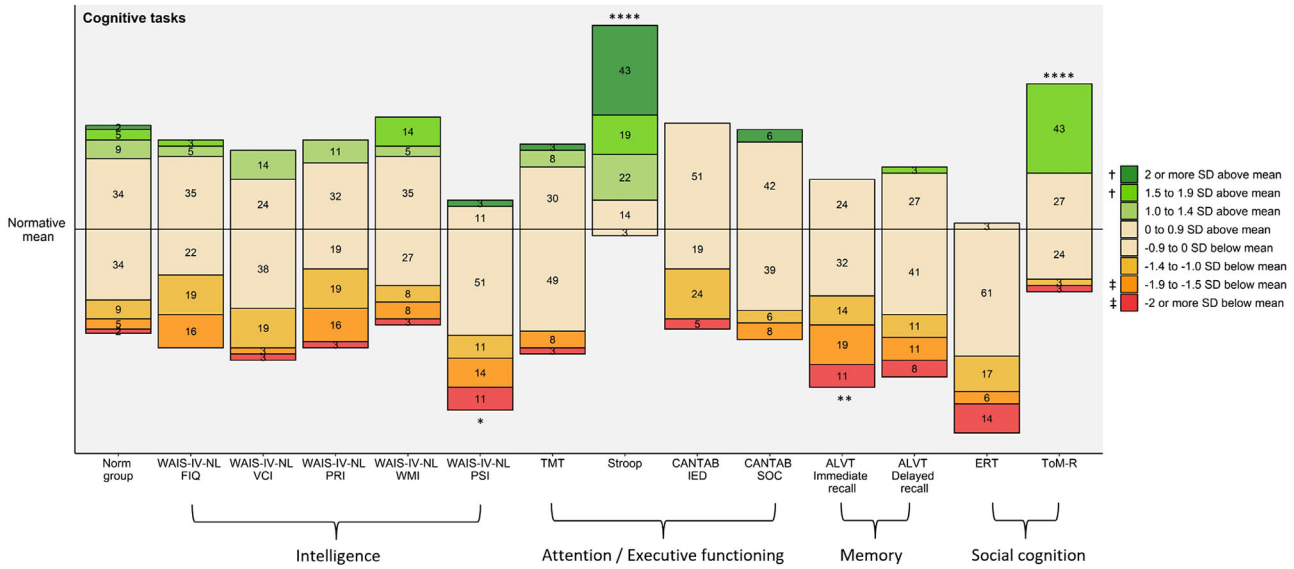

FIGURE 1 Cognitive task scores in adults with PHTS, compared to norm scores. The numbers represent percentages of participants. Reddish color indicates lower performance. †Above average; ‡below average. *<0.10, **<0.05, ***<0.01, and ****<0.001. AVLT, auditory verbal learning task; CANTAB, Cambridge Neuropsychological Test Automated Battery; ERT, emotion recognition task; FIQ, full-scale IQ; IED, intra/extradimensional shifting task; PHTS, PTEN hamartoma tumor syndrome; PRI, perceptual reasoning index; PSI, processing speed index; SD, standard deviation; SOC, stockings of Cambridge; TMT, trail making test; ToM-R, Dutch Theory of Mind test revised; VCI, verbal comprehension index; WAIS-IV-NL, Wechsler Adult Intelligence Scale-IV-NL; WMI, working memory index.

TABLE 3 Questionnaire scores in adults with PHTS, compared to norm scores (presented as *z*-scores).

Measure	*N*	Mean (SD)	Min	Max	Median	% below average, <−1.5 SD (expected % in norm group)	% average, −1.5 to 1.5 SD (expected % in norm group)	% above average, >1.5 SD (expected % in norm group)
Psychological and physical functioning								
SCL-90 psychoneuroticism	39	0.90 (1.46)	−0.78	4.99	0.45	0.0 (7)	74.4 (86)	**25.6 (7)****
Subscales								
Anxiety	39	0.76 (1.45)	−0.62	6.18	0.51	0.0 (7)	76.9 (86)	23.1 (7)*
Agoraphobia	39	0.53 (1.50)	−0.37	6.90	0.06	0.0 (7)	82.1 (86)	17.9 (7)
Depression	39	0.76 (1.45)	−0.74	5.48	0.32	0.0 (7)	76.9 (86)	23.1 (7)*
Somatization	39	0.56 (1.21)	−0.88	3.62	0.25	0.0 (7)	79.5 (86)	20.5 (7)
Cognitive performance deficits	39	1.20 (1.69)	−0.85	5.50	0.56	0.0 (7)	64.1 (86)	**35.9 (7)*****
Interpersonal sensibility	39	0.62 (1.37)	−0.79	5.23	0.26	0.0 (7)	79.5 (86)	20.5 (7)
Anger—hostility	39	0.40 (1.12)	−0.58	4.66	−0.10	0.0 (7)	87.2 (86)	12.8 (7)
Sleeping difficulties	39	1.00 (1.44)	−0.66	4.79	0.70	0.0 (7)	66.7 (86)	**33.3 (7)*****
Emotion regulation								
FEEL-E adaptive strategies	39	−0.09 (1.46)	−3.00	3.00	−0.30	15.4 (7)	69.2 (86)	15.4 (7)
FEEL-E maladaptive strategies	39	−0.66 (1.17)	−2.50	2.50	−0.60	**35.9 (7)*****	59.0 (86)	5.1 (7)
Alexithymia								
TAS-20	39	0.72 (1.19)	−1.86	3.48	0.72	5.1 (7)	71.8 (86)	23.1 (7)*
Cognitive problems								
BRIEF-A	39	0.66 (1.15)	−1.00	3.50	0.60	0.0 (7)	76.9 (86)	23.1 (7)*

Note: A higher mean indicates more problems reported. *<0.10, **<0.05, ***<0.01, and ****<0.001 based on Chi-squared tests.
Abbreviations: BRIEF-A, Behavior Rating Inventory of Executive Function-Adult Version; FEEL-E, Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen; PHTS, PTEN hamartoma tumor syndrome; SD, standard deviation; SCL-90, symptom checklist-90-R; TAS-20, Toronto Alexithymia Scale.

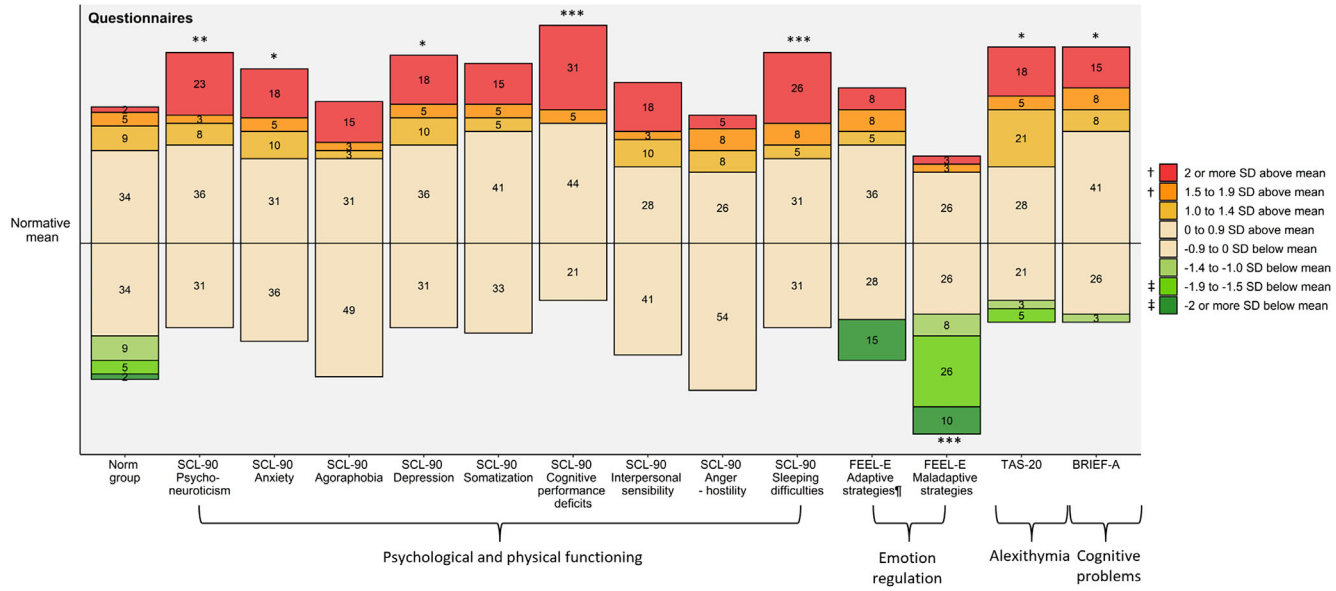

FIGURE 2 Questionnaire scores in adults with PHTS, compared to norm scores. The numbers represent percentages of participants. Reddish color indicates more problems reported. ¶ scores on this task were mirrored to match the legend. †Above average; ‡below average. *<0.10, **<0.05, ***<0.01, and ****<0.001. BRIEF-A, Behavior Rating Inventory of Executive Function-Adult Version; FEEL-E, Fragebogen zur Erhebung der Emotionsregulation bei Erwachsenen; PHTS, PTEN hamartoma tumor syndrome; SCL-90, Symptom Checklist-90-R; SD, standard deviation; TAS-20, Toronto Alexithymia Scale.

TABLE 4 SWAP-200-NL scores in adults with PHTS (presented as *T* scores).

Measure	*N*	Mean (SD)	Min	Max	Median	% average *T* = 0–55	% clinically significant "features" *T* ≥ 55	% clinically significant *T* ≥ 60
Personality traits								
SWAP-200-NL factor *T*-scores								
Psychological health	39	79.13 (7.24)	60.30	87.70	81.30	0.0	100.0	100.0
Psychopathy	39	45.62 (1.80)	42.10	51.60	45.20	100.0	0.0	0.0
Hostility	39	36.83 (5.38)	27.70	49.10	36.10	100.0	0.0	0.0
Narcissism	39	43.05 (4.04)	40.00	58.90	41.80	97.4	2.6	0.0
Emotional dysregulation	39	45.72 (7.58)	33.60	62.20	46.90	87.2	12.8	5.1
Dysphoria	39	43.80 (7.46)	33.50	61.80	43.50	92.3	7.7	2.6
Schizoid orientation	39	51.48 (9.05)	38.30	75.50	52.00	71.8	28.2	12.8
Obsessionality	39	57.35 (5.30)	45.50	71.10	57.40	35.9	64.1	33.3
Thought disorder	39	46.70 (5.21)	41.20	64.80	45.70	94.9	5.2	2.6
Oedipal conflict	39	41.12 (2.48)	37.70	52.30	39.70	100.0	0.0	0.0
Dissociation	39	52.03 (9.43)	38.70	77.70	51.20	66.7	33.3	25.6
Sexual conflict	39	42.97 (3.82)	40.10	53.90	40.40	100.0	0.0	0.0

Note: A higher mean indicates more traits reported.
Abbreviations: PHTS, PTEN hamartoma tumor syndrome; SD, standard deviation; SWAP-200-NL, Shedler-Western Assessment Procedure (Dutch version).

schizoid orientation (13%) (Table 4 and Figure 3). To gain a better understanding of the meaning of these traits, the items were ranked from lowest to highest (Table S1). The highest ranked items on the psychological health index were the tendency to be conscientious and responsible, having moral and ethical standards, and the tendency to elicit liking in others. The obsessionality, items that ranked highest included the tendency to adhere rigidly to daily routing, be excessively devoted to work and productivity, and the tendency to be overly concerned with rules, procedures, order, organization, or schedules. Dissociation referred mainly to the tendency to describe experiences in generalities, to have difficulties reproducing (distressing) memories, and to experience the past as a series of disconnected events. Finally,

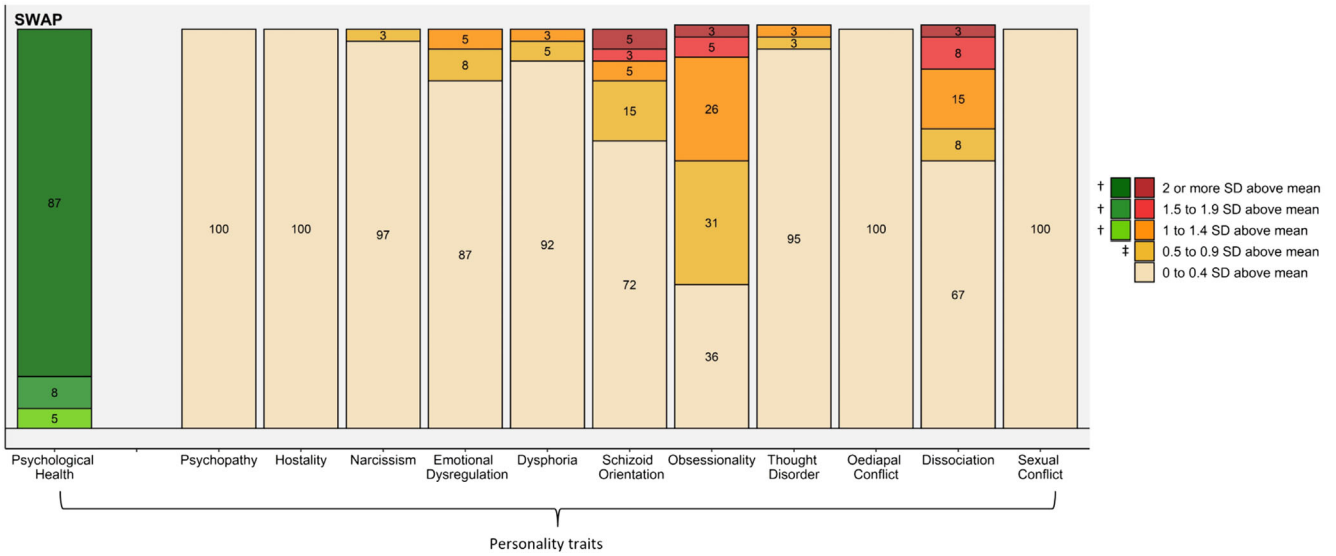

FIGURE 3 Personality traits in adults with PHTS. The numbers represent percentages of participants. Greenish and reddish colors indicate a specific personality trait. †Clinically significant personality trait; ‡clinically significant features of a personality trait. PHTS, PTEN hamartoma tumor syndrome; SD, standard deviation; SWAP-200-NL, Shedler-Western assessment procedure (Dutch version).

the highest ranked items on schizoid orientation included the lack of close friends and relationships, little need for human company or contact, and the tendency to think in concrete terms.

3.4 | Cognitive and behavioral observations

Based on the summed scores of the observation checklist (Table S2), a high proportion of participants were frequently concerned about neatness, orderliness, and order (50%), showed a lack of confidence (32%), felt easily embarrassed (19%), were afraid of making mistakes (16%), or asked for feedback (16%). Furthermore, problems in fine motor dexterity (21%, e.g., slow motor skills, mild tremor) and noticeable differences in speech and voice (24%, e.g., loud voice, deviating tempo or tone) were frequently observed. A high proportion of participants (26%) showed increased tiredness during the 3–4 h cognitive assessment. Finally, attentional and executive problems were observed frequently during the assessment, which included overlooking mistakes (18%), an impulsive approach (16%), and having difficulties switching between tasks or conversations (16%).

3.5 | Secondary analyses

No statistically significant or clinically relevant differences in cognitive or psychological functioning between index versus non-index patients were found.

4 | DISCUSSION

Our study is the first to extensively explore the neuropsychological functioning of a relatively large group of adults with PHTS and describes unique data that can be used to compile strategies on how to further improve the care and daily lives of individuals with PHTS. Our findings demonstrate a distinct yet heterogeneous neuropsychological profile in our adult PHTS cohort, with vulnerabilities that could lead to psychological problems and ineffective clinician–patient interaction.

Regarding cognitive functioning, mean full-scale IQ scores in our adult PHTS cohort, with intellectual disability as exclusion criterium, showed an average intelligence level that varied widely from below to above average. Our findings are in line with results from a predominantly adult PHTS cohort reported by Busch et al. (2013) and complement the existing literature, which often portrays intellectual disability as a prevalent manifestation of the PHTS phenotype. Furthermore, an average performance on Stroop card III and a low average performance on Stroop card I and II were noted. This suggests a slow pace of word reading and color naming, which could possibly be explained by reading difficulties, slowed visual information processing, or observed oral motor functioning (Ekinci et al., 2021; Proulx & Elmasry, 2015). In addition, a substantial part of adults with PHTS showed lower performance on immediate memory recall and speed of information processing, which have been observed to varying degrees in previous studies and mostly in PHTS individuals with ASD (Balci et al., 2018; Busch et al., 2019; Plamper et al., 2020). These results may suggest an underlying slow speed of information processing, which can lead to multiple frailties such as delayed reaction time, difficulty understanding extensive and complex information, lower cognitive performance in other domains, fatigue, and difficulties during daily activities (Bucur et al., 2008; Salthouse, 2005). On that premise, the slow information processing speed might explain the observed difficulties in immediate memory recall, the cognitive complaints based on the SCL-90 and BRIEF-A, and the systemic observations pointing toward an impulsive approach, overlooking mistakes, difficulties switching between tasks or conversations, and increased tiredness.

As to psychological functioning, a high number of adults with PHTS reported subjective executive problems, signs of alexithymia (i.e., difficulty recognizing and describing one's own emotions), and emotional and physical complaints including anxiety, depression, cognitive deficits, and sleeping difficulties. These findings are generally consistent with previous, though limited, studies on psychological problems in individuals with PHTS (Balci et al., 2018; Busch et al., 2019; Hansen-Kiss et al., 2017). Regarding personality, a substantial proportion of adults with PHTS showed traits of obsessionality, dissociation, and schizoid orientation. Obsessionality can be viewed as a tendency toward inflexible thinking and excessive concern about rules and procedures (Shedler & Westen, 2007). Dissociation refers to having disconnected thoughts and feelings, which is consistent with the high frequency of alexithymic features. The schizoid orientation trait overlaps with the former two traits in the tendency toward intellectualizing and prioritizing a more rational approach over an emotional approach, though it also describes a tendency to social withdrawal. Literature has shown that these traits show considerable overlap with each other and can occur both individually and together. For example, alexithymia may result in reduced flexibility in thinking and behavior and a tendency toward rigidity and inflexibility in response to stressful situations, which can manifest in rigid behaviors and attitudes (Giles et al., 2020; Lumley et al., 2007). It could be argued that these personality traits of inflexibility, social withdrawal, and difficulties in recognizing and describing one's own emotions share some similarities with ASD, which is a commonly described classification in individuals with PHTS. Alexithymia, for instance, shares considerable overlapping traits with ASD, such as difficulties in identifying and describing emotions (Poquérusse et al., 2018). It is, however, important to note that there are also distinct differences and that alexithymia can be viewed as an independent construct having its own neurocognitive and etiological basis (Shah et al., 2016).

Taken together, the slower speed of information processing, the personality traits of inflexible and controlling behavior, the tendency toward abstract and intellectual thinking, and the difficulties in recognizing and describing emotions suggest that many adults with PHTS may struggle to adapt to new, unexpected, stressful, or emotional situations. This, together with the stressful and emotional events that patients may face during life (e.g., (fear of) developing cancer, (fear of) passing on the *PTEN* variant in the offspring, and (fear of) loss of family), could make them more vulnerable to psychological problems. Indeed, we observed a high frequency of adults in our cohort with a psychological (treatment) history and reported psychological complaints on the SCL-90. Based on this reasoning, the identified neuropsychological vulnerabilities could potentially have a negative impact on patients' lives.

The neuropsychological vulnerabilities observed in adults with PHTS can potentially also lead to ineffective clinician–patient interaction. Regarding cognitive functioning, the lower performance on memory recall and speed of information processing may result in information not being properly absorbed, comprehended, or expressed. This could hamper effective clinician–patient interaction and might explain the difficulties in providing information and problematic communication observed in the pilot study. To enhance clinician–patient interaction, clinicians may consider slowing down their pace of information exchange, use visual information aids such as pictures and charts, and provide written materials such as brochures and handouts to supplement verbal communication. Regarding psychological functioning, the personality traits of inflexible and controlling behavior, the tendency toward abstract and intellectual thinking, and the difficulties in recognizing and describing own emotions might also hamper effective clinician–patient interaction. People with these traits might be self-critical and deny their own need for care or consider such needs as unnecessary, and might be more inflexible and controlling in their communication resulting in clinician–patient miscommunications (Shedler & Westen, 2007). An interpretive approach aimed at (a) helping individuals recognize and understand their thoughts and feelings, for example, by giving them sufficient time to respond, (b) encourage them to express their thoughts and concerns, and (c) show interest and understanding, might optimize the clinician–patient interaction (Shedler & Westen, 2007). Finally, clinicians could consider a referral for individual clinical neuropsychological assessment in a selection of individuals with PHTS who are hindered by cognitive or psychological complaints. Importantly, the heterogeneous neuropsychological profile in combination with the unique environmental context for each individual implies that the need and extent of psychosocial guidance in adults with PHTS should be tailored to a one-by-one case.

This study is the first to extensively explore the neuropsychological functioning of a large group of adults with PHTS at our PHTS expertise center, when acknowledging the rarity. All measurements were performed and scored by the same psychologist, which minimizes the inter-observer variability. Another strength is the multimethod clinical neuropsychological assessment, which included the use of cognitive tasks, questionnaires, systemic observations, and the SWAP-200-NL. The SWAP-200-NL combines clinical assessment with empirical research, which, in combination with the other methods, provides psychologically rich descriptions of individuals. One of the limitations is that the study population might not be fully representative of the overall adult PHTS population, as individuals with intellectual disability were excluded. This may have caused a bias toward a more favorable neuropsychological functioning. Furthermore, this study did not include a control group. Future studies might consider including individuals with another rare genetic (tumor risk) syndrome as these individuals may share a more or less similar somatic or psychological burden. Future research on the neuropsychological functioning of individuals with PHTS is essential to confirm our findings. Besides studies with a cross-sectional design, longitudinal studies could provide additional knowledge about the neuropsychological functioning of PHTS, for example, about whether the level of functioning changes over time.

In conclusion, this study, with intellectual disability as exclusion criterium, identified a heterogeneous yet distinct neuropsychological profile in adults with PHTS that is characterized by an average level of

intelligence, a slower speed of information processing, psychological problems, inflexibility, social withdrawal, and difficulties in recognizing and describing their own emotions. These vulnerabilities could lead to ineffective clinician–patient interaction and negatively impact patients' day-to-day lives, and therefore warrant timely evaluation and optimization of psychosocial guidance in individuals with PHTS. Clinicians could consider slowing down their speaking pace, provide visual or written information, and encourage patients' expression of feelings and thoughts, to optimize patient care.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: NH, JE, TK, JP, LvD, CO, and MD. *Investigation and formal analysis*: CO and MD. *Writing—original draft*: CO and MD. *Writing—review and editing*: NH, JE, TK, JP, and LvD. *Supervision*: NH and LvD.

ACKNOWLEDGMENTS

This study was funded by a grant from the Radboud Oncologie Fonds.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Oldenboom, C., Drissen, M. M. C. M., L. C. M. van Dongen, Kleefstra, T., Prins, J. B., Egger, J. I. M., & Hoogerbrugge, N. (2024). Neuropsychological functioning of adults with *PTEN* hamartoma tumor syndrome. *American Journal of Medical Genetics Part A*, e63653. https://doi.org/10.1002/ajmg.a.63653