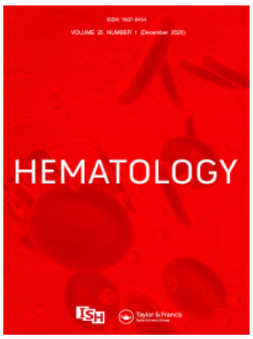

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REVIEW ARTICLE

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Measuring the neuropsychological consequences of thrombotic thrombocytopenic purpura: a rapid literature review

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ABSTRACT

Objectives: Thrombotic thrombocytopenic purpura (TTP) is a hematological disorder associated with potentially severe long-term health outcomes, including neuropsychological consequences. Guidelines recommend cognitive assessment for people with TTP, and an understanding of how the condition affects various cognitive domains can support decision-making for clinicians when selecting assessment measures.
Methods: A rapid literature review was conducted using MEDLINE Ultimate, CINAHL Ultimate and PsycINFO to appraise the existing evidence base regarding the impact of TTP on cognition, the measures used to assess cognitive impairment, and the correlates of cognitive impairment in this population group.
Results: Fourteen articles were eligible for inclusion and the results were summarized using a narrative synthesis. TTP is associated with impairment across all assessed cognitive domains. Cognitive impairment is associated with abnormal cerebral findings but not ADAMTS13 levels or severity and frequency of acute episodes. The sensitivity of brief screening measures in detecting TTP-related cognitive change is unclear.
Conclusion: Comprehensive cognitive assessment following TTP, including an exploration of possible confounding factors such as poor mental health, is recommended. Caution when relying on brief screening measures is advised.

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KEYWORDS
Thrombotic thrombocytopenic purpura; TTP; cognition; neuropsychological impact; neuropsychological consequences; cognitive impairment

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening hematological disorder that occurs as a result of a severe deficiency in *ADAMTS13* ('a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13'), a metalloprotease enzyme that helps to regulate blood clotting by cleaving von Willebrand factor (vWF) [1]. TTP can be congenital (cTTP) or acquired (iTTP) due to the production of anti-ADAMTS13 autoantibodies [2]. Some of the symptoms of TTP include low platelet count, petechiae and purpura, paleness or jaundice, extreme tiredness, and neurological symptoms such as confusion, seizure or stroke [3].

Both forms of TTP are considered rare; estimates of prevalence globally range from 0.4 to 16.7 per million for cTTP and 3.43 to 21.44 per million for iTTP [4], with the condition being more prevalent amongst Black people and women [5,6]. Whilst it is rare, the impact and burden of TTP can be severe. Neurological complications such as stroke [7], hypertension [8], depression and post-traumatic stress disorder [9,10] are not unusual following TTP, significantly affecting quality of life.

Due to the seriousness and long-term burden of TTP, the National Health Service (NHS) has commissioned nine specialist TTP centres across England, allowing all patients with TTP to be registered for treatment and follow-up at their closest centre [11]. It is also now well-established that TTP is associated with cognitive impairment [12], though the extent and breadth of this impairment, as well as its trajectory over time, remains an open question. The British Society for Haematology recommends that cognitive assessment should be offered for people with TTP where appropriate [13], yet little is known about what specific measures may be useful in detecting TTP-related cognitive change, which subgroups may particularly benefit from assessment, and

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which domains of cognition may be particularly affected. Understanding the existing evidence base in relation to these issues would support clinicians in decision-making regarding the offer of cognitive assessment.

The aim of this rapid review is to therefore understand what the neuropsychological consequences of TTP are, how these consequences have been measured, and what factors have been identified in the literature as being correlated with cognitive impairment in TTP. Rapid literature reviews employ a simplified approach to a systematic review protocol, focusing on a narrower scope of literature and making use of specific methodological shortcuts whilst also ensuring high standards of scientific rigour are maintained [14]. The purpose of this project is to inform clinical practice in TTP centres, equipping practitioners with an understanding of the existing evidence base as well as relevant factors to consider when assessing cognition post-TTP.

Method

This review was conducted in line with recommendations and considerations from The Cochrane Rapid Reviews Methods Group [15], adopting a simplified approach to the traditional systematic review whilst still maintaining a high level of rigour.

Search strategy

A systematic search of the literature was conducted on 28th April 2025 and updated on 17th November 2025. EBSCOHost was used to search the following databases: MEDLINE Ultimate, CINAHL Ultimate and PsycINFO. The following search terms were used: *(neuropsycholog* OR cogn*) AND (thrombotic thrombocytopenic purpura)*. Specific search terms were used to capture a comprehensive range of relevant results, ensuring this rapid review could be completed in a timely manner. Reference lists of eligible papers were manually searched and a supplementary search using Google Scholar was also completed.

Eligibility criteria

English-language articles published in peer-reviewed journals from inception until 17th November 2025 were eligible for inclusion in this review. To be included, human participants diagnosed with any subtype of TTP should have completed at least one self-administered or clinician-administered measure of cognitive function, encompassing at least one or more of the cognitive domains listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5; [16]): complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. Literature reviews were excluded to avoid duplication of findings, and articles where details of the measures and/or results are not reported were also excluded.

Screening and selection

Following the removal of duplications, titles and abstracts of all studies were screened by the first reviewer (lead author) to determine if an article should proceed to a full-text review. The second reviewer (second author), blind to the lead author's ratings, independently screened 20% of retrieved records. Disagreements were discussed and resolved with consideration of the eligibility criteria.

Data extraction

Data extraction was completed by the lead author with the second author cross-checking the extracted information for 20% of the studies. The names of all administered cognitive measures were extracted, as well as the studies' reported findings regarding the cognitive assessment. The following data was also extracted from each study: Authors, year of publication, study design, country, control group if applicable, TTP subtype, sample size, time since last acute episode, and age.

Quality appraisal

Quality assessment was conducted using the Joanna Briggs Institute (JBI) quality appraisal tools for cross-sectional or cohort studies [17]. The cross-sectional study checklist contains eight items whereas the cohort study checklist contains 11 items, with nominal responses of 'Yes', 'No', 'Unclear' or 'Not applicable' provided for each item. The tools do not provide an overall rating for each study but instead facilitate careful critical evaluation of a study's strengths and weaknesses.

Results

Search results

The search strategy yielded 76 results after the removal of duplicates, with one additional paper identified through a citation search. Following title and abstract screening, 38 articles proceeded to full-text review, of which 24 articles were excluded. The inter-rater agreement rate was approximately 90%, with consensus reached in all instances following discussion. In most cases, articles were excluded due to being a review or an opinion piece, or due to a lack of cognitive measures being administered in the study (see Figure 1). Fourteen articles were eligible for inclusion in the final review.

Study characteristics

Individual study characteristics are reported in Table 1. The majority of studies (9/14) utilized a cross-sectional design; amongst these studies is one study [19] which contains some results that can be compared

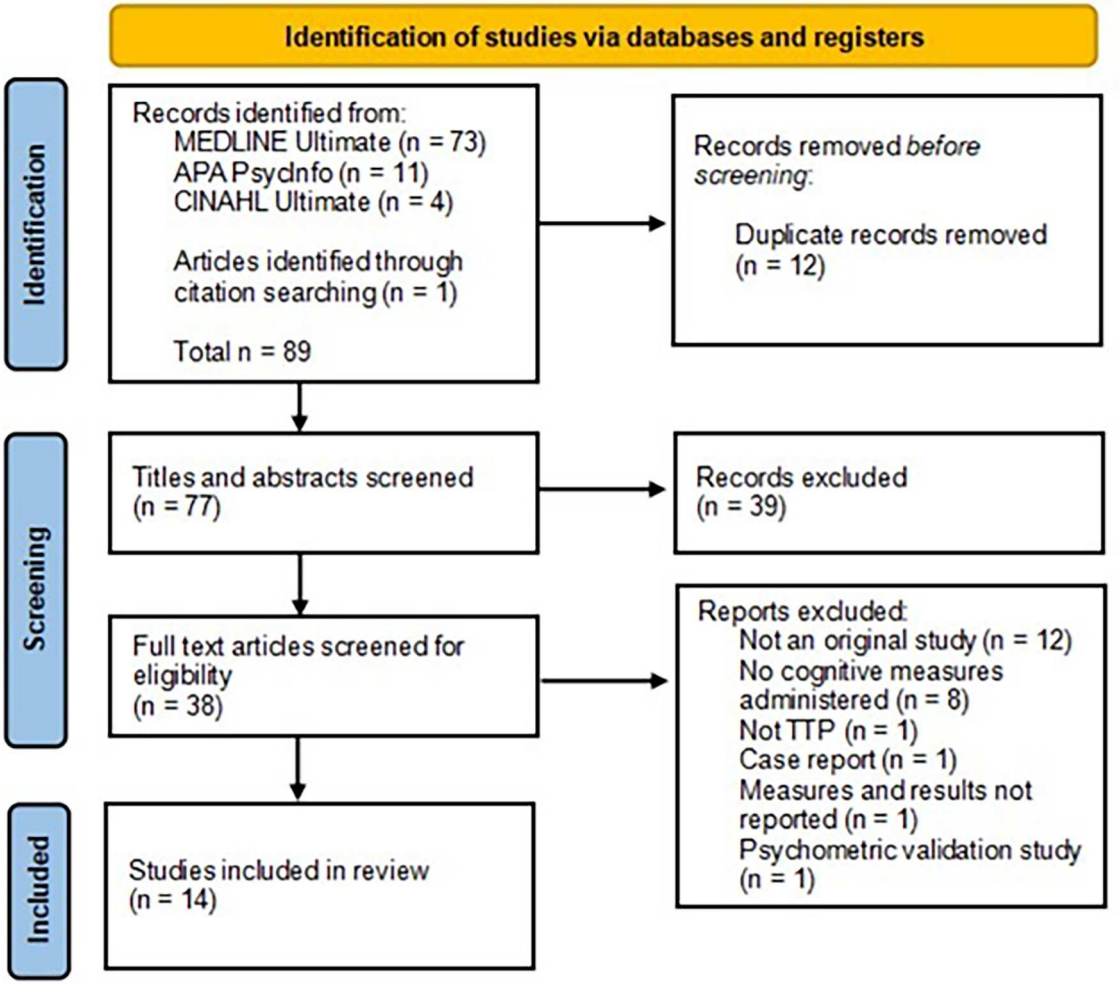

Figure 1. Flowchart of the study identification, screening and inclusion/exclusion process. Adapted from Page et al. [18].

Table 1. Study characteristics of the included articles.

Authors	Year	Study design	Country	Healthy controls sample size	TTP type	TTP sample size completing tests	Age (years, median)
Alwan et al.	2020	Cross-sectional	UK	N/A	iTTP and cTTP	35	Not reported
Boothby et al.	2025	Cohort	USA	N/A	iTTP	33	Not reported
Chaturvedi et al.	2023	Cross-sectional (baseline data)	USA	N/A	iTTP	42	48
Falter et al.	2017	Cohort	Germany	52	iTTP and cTTP (n = 1 for cTTP group)	101	46 and 45 (two surveys)
Falter et al.	2021	Cohort	Germany	134	iTTP	Unclear, total sample = 104	48 and 51 (two surveys)
Han et al.	2015	Cross-sectional	USA	N/A	iTTP	35	Not reported
Hannan et al.	2024	Cross-sectional	Canada	6	iTTP	20	53
Holmes et al.	2021	Cross-sectional	UK	N/A	iTTP	50	Not reported
Kennedy et al.	2009	Cross-sectional	USA	N/A	iTTP	24	44
Mulas et al.	2024	Cross-sectional	Italy	N/A	iTTP	38	50
Riva et al.	2020	Cross-sectional	Italy	N/A	iTTP	35	45
Scully et al.	2022	Cohort	Worldwide	N/A	iTTP	Unclear, total sample = 104	Not reported for whole group
Selvakumar et al.	2025	Cross-sectional	USA	N/A	iTTP	40	51
Yu et al.	2025	Cohort	USA	N/A	iTTP	42 for visit 1, 28 for visit 2	47.5 and 48 (two visits)

to a previous publication [20]. Only 5/14 studies utilized a cohort design, which would allow for follow-up testing and measuring change over time, including one study [21] monitoring patients who had previously been randomly allocated to Caplacizumab or placebo in a separate clinical trial. One additional study [22] reports baseline results that are followed up in a separate publication [23]. A further two studies [19,24] report the administration of clinician-administered neuropsychological measures at multiple timepoints, although in one study [24] follow-up results are not reported.

The majority of studies (10/14) administered clinician-led neuropsychological measures. Most studies (12/14) included only individuals with iTTP; whilst two studies also included individuals with cTTP [25,26], it is unclear how many individuals with cTTP undertook the cognitive assessment (although in both studies the vast majority of participants were diagnosed with iTTP). Healthy controls were utilized in just 3/14 studies. Sample size, median age, gender split, and average duration of remission varied widely across studies, and the reporting of demographic information was often incomplete (see Table 1 for details).

Risk of bias

Many studies utilized small sample sizes with no or few controls, likely affecting statistical power (see Table 1). Inclusion and exclusion criteria were generally well defined, however, confounding variables were often not identified or addressed. Objective criteria in confirming the diagnosis of TTP were frequently used. Established tools to measure the outcome of interest (i.e. cognitive changes) were used by all studies, however, none of these measures have been specifically validated for use in TTP. Reporting of power, probability values and effect sizes is inconsistent across and within studies. Individual responses to critical appraisal checklist items per study are presented in Supplementary File 1.

Measures used to assess cognitive performance

The majority of studies conducted comprehensive assessments encompassing various cognitive domains, with the exception of social cognition, which was not reported to be evaluated in any study (see Table 2 for a list of measures and headline findings across studies). Cognitive domains assessed in the literature included attention, executive function, language, learning/memory, and perceptual motor skills.

Brief screening tools and estimates of premorbid functioning

Brief screening measures were utilized by 3/14 studies: Kennedy et al. [20] administered the Mini-Mental State Examination (MMSE; [33]), and all participants who undertook neuropsychological assessment

Table 2. Clinician-administered and self-reported measures used, direction of main findings and time since last acute TTP episode across studies. SD = standard deviation.

Study	Clinician-administered measures used and domains tested	Self-reported measures used and domains tested	Comparator	Direction of findings	Time since episode
[25]	Premorbid Intelligence: NART Intelligence: WAIS-III Memory: RMT – Words & Faces, RMT – Topographical, Adult Memory and Information Processing Battery, Doors & People Test Language: Graded Naming Test Executive Function: Stroop Colour Word Test, Phonemic Fluency (FAS & Animals), Cognition Estimation Test, Modified Card Sorting Task, Hayling Test Processing Speed: 'A' and 'O' cancellation tests, Symbol Digit Modalities Test		Normative scores	Executive function impairment and memory impairment observed in 63% and 57% of participants respectively (performance at or below tenth percentile or below cutoff scores) Intellectual impairment in 43% (decline of 1 SD or more between NART and WAIS) Those with abnormal MRI findings had significantly lower Performance and verbal IQ, with frontal lobe abnormalities particularly associated with intellectual impairment	Mean = 33 months
[24]	Screening: MoCA Attention and Processing Speed: CPT-3 Learning and Memory, Language, Attention, and Visuospatial Processing: RBANS		Normative scores	26% had slower reaction times (1–2 SD below norm) on the CPT-3 'Marked' deviations (z-score = ≥ -1) for immediate memory and visuospatial construction on the RBANS	Median = 6.3 years
[22]	Episodic and Working Memory, Language, Executive Function, Attention, Processing Speed: NIH Toolbox Cognition Battery	'Mental acuity', Concentration, Verbal and Nonverbal Memory, and Verbal Fluency: PROMIS Cognitive Function Form 8a	Normative scores	52.3% had impairment in at least one domain (1 SD or more below norm)	Not reported
[26]		Attention, Memory and Executive Function: FLei	Control group of healthy adults	Mental performance and all 3 sub-scores significantly worse than controls, but better than depressed individuals' performance in wider literature	Not reported
[27]		Attention, Memory and Executive Function: FLei	Control group of healthy adults age and gender matched	FLei scores significantly worse than controls Perceived cognitive performance reduced for iTTP group	Not reported
[19]	Screening: MoCA Learning and Memory, Language, Attention, and Visuospatial Processing: RBANS		Normative scores	MoCA and all RBANS scores significantly lower than general population (all mean RBANS scores were within 1 SD of norm)	Not reported
[28]	Memory, Visuospatial Processing, Language, Attention: Cambridge Brain Sciences Health Assessment		Control group of healthy adults	Significant impairment (1 to 2 SD below healthy controls) in verbal memory, one short term memory subtest and concentration Other results not significantly different to controls	Not reported
[29]		'Mental acuity', Concentration, Memory, Verbal Fluency: PROMIS Cognitive Function Abilities subset Short Form 6a	Normative scores	PROMIS results show impairment (Mean score 1 SD below norm)	Not reported
[20]	Screening: MMSE Premorbid Intelligence: OPIE-3 Intelligence: WAIS-III Matrix Reasoning and Vocabulary subtests (as part of OPIE-3) Learning and Memory: WMS-R Logical Memory and Visual Reproduction subtests, CVLT-II Free Recall subtests Attention: Conners Continuous Performance Test, Trail Making Test		Normative scores	No differences observed on the MMSE and OPIE-3 75% demonstrated impairment (1 SD or more below mean) in at least one of four domains: complex attention and sequencing, manual dexterity, rapid language generation and list learning	Median = 4 years

(*Continued*)

Table 2. Continued.

Study	Clinician-administered measures used and domains tested	Self-reported measures used and domains tested	Comparator	Direction of findings	Time since episode
	Processing Speed: CCPT, Grooved Pegboard Test Visuospatial Processing: Symbol Digit Modalities Test, Hooper Visual Organization Test Executive Function: DKEFS Design Fluency Subtest Language: Phonemic Fluency test, Semantic Fluency Test Perceptual-motor Function: Grooved Pegboard Test				
[30]		Attention, Memory, Language, Processing Speed, Executive Function: FACT-Cog	Normative scores	FACT-Cog scores significantly correlated with other measures of mental health and health-related quality of life	Median = 41 months
[31]	Memory: Digit Span, Rey Word List (RAVLT) Attention: Trail Making A, Trail Making B		Normative scores	Mean memory and attention scores significantly lower than norms	Median = 3 years
[21]	Learning and Memory, Language, Attention, and Visuospatial Processing: RBANS		Caplacizumab vs placebo groups	No 'clinically meaningful difference' (8 points) between groups on any RBANS changes at follow-up	Not reported
[32]	Working Memory, Language, Executive Function, Attention, Processing Speed: NIH Toolbox Cognition Battery		Normative scores	53% scored in the 'mild' cognitive impairment range (1–2 SD below mean) in at least one domain on the NIH Toolbox 27% scored in the 'major' cognitive impairment range (>2 SD below mean)	Not reported
[23]	Episodic and Working Memory, Language, Executive Function, Attention, Processing Speed: NIH Toolbox Cognition Battery		Normative scores	Cognitive function did not significantly change after one year for the overall sample Cognitive scores improved significantly in people with TTP who did not present with progression in Silent Cerebral Infarction	Not reported

scored in the normal range. However, individuals who scored less than 24 on the MMSE were excluded, possibly skewing the sample by excluding participants with major impairment. Two studies [19,24] administered the Montreal Cognitive Assessment (MoCA; [34]). Han et al. [19] found that participants' MoCA scores were significantly lower than the reference population data with a mean score of 25.2 (95% confidence intervals: 24.1–26.3. Referenced population norm = 27.4). Moreover, performance on the MoCA correlated with performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; [35]). Boothby et al. [24] did not report data on participants' MoCA performance.

Only 2/14 studies utilized estimates of premorbid intelligence to ascertain if neuropsychological findings could be directly attributed to the impact of TTP. Kennedy et al. [20] used the Oklahoma Premorbid Intelligence Estimate-III (OPIE-3), an algorithm combining scores on the matrix reasoning and vocabulary subtests of the Weschler Intelligence Scale – Third Edition (WAIS-III; [36]) with demographic information to estimate premorbid intellectual functioning [37]. Alwan et al. [25] utilized the National Adult Reading Test (NART), a tool that estimates premorbid intellectual functioning by assessing reading ability [38]. In both studies, participants were estimated to have within 'normal range' premorbid functioning, supporting the assertion that any deficits in cognitive performance may be attributable to TTP in these studies' samples.

Cognitive performance in TTP

Across all studies utilizing clinician-administered measures, participants with TTP exhibited cognitive impairment in at least one domain compared to controls or standardized norms. In studies where participants completed self-reported measures of cognitive functioning, participants frequently reported poorer cognitive functioning relative to healthy controls.

Compared to norm-referenced data rather than controls, Kennedy et al. [20] found that on average, people with TTP were significantly impaired on measures of complex attention, language generation, manual dexterity and list learning, with 75% of tested individuals being impaired in at least one domain. Riva et al. [31] indicated that on average, people with TTP were impaired on tests of verbal memory but performed inconsistently on measures of attention. However, effect sizes and probability values for the cognitive assessment are not reported, making it difficult to draw conclusions.

Alwan et al. [25] administered a comprehensive assessment of current intellectual functioning, finding that 43% of individuals with TTP exhibited overall intellectual impairment as defined by a difference of one standard deviation (SD) or more between estimated premorbid intelligence and current intelligence quotient (IQ) on the WAIS-III. Performance IQ (P-IQ), a measure of perceptual reasoning and processing speed abilities, was more likely to be impaired than Verbal IQ (V-IQ), a measure of verbal comprehension and working memory abilities. However, effect sizes and probability values were again not reported. Hannan et al. [28] administered the Cambridge Brain Sciences test (now called Creyos; [39]), an online cognitive assessment which consists of 12 tasks across four subdomains (short-term memory, verbal memory, perceptual reasoning and concentration). The results indicated significant impairment in verbal memory and concentration, as well as one test of short-term memory. However, the researchers note that the study is underpowered, potentially affecting the validity of statistical analyses.

3/14 studies [19,21,24] administered the RBANS. Compared to normative data, Boothby et al. [24] found participants exhibited significant impairment overall as well as on the immediate memory and visuospatial/construction domains. The researchers also report that RBANS scores did not differ significantly on annual reviews, though data for these are not included. Similarly, Han et al. [19] found that on average, participants exhibited significant impairment on all RBANS cognitive domains as well as on the overall score. For participants who had previously completed comparable measures in 2006 [20] Han et al. [19] found that overall RBANS scores as well as the immediate and delayed memory scores (all age-standardized) had significantly declined over time, indicating a change in performance beyond what would have been expected due to normal ageing.

Scully et al. [21] reported that differences in RBANS scores between individuals who had been randomly allocated to Caplacizumab or placebo during an acute episode of iTTP did not reach clinical importance at 36-month follow-up. However, whilst all mean RBANS scores in both groups were within one SD of the norm

at both baseline and follow-up, the researchers do not report whether differences in scores between the groups reached statistical significance on any domain. No other study reported sub-group analyses for individuals administered anti-vWF therapy.

3/14 studies [22,23,32] utilized the National Institute of Health (NIH) Toolbox Cognition Battery, a comprehensive set of tests covering various cognitive domains and administered via an iPad [40]. Chaturvedi et al. [22] found that 52.3% of people with TTP presented with cognitive impairment in at least one cognitive domain, with deficits occurring most commonly in executive function and processing speed. Similarly, Selvakumar et al. [32] found that 53% of people with TTP in their sample presented with cognitive impairment in at least one domain on the NIH Toolbox, though it should be noted that both studies recruited from the same population (patients followed at Johns Hopkins University). Crucially, these results highlight the fact that not all individuals with TTP will exhibit cognitive impairment. However, reliable data on how large this group may be is limited.

Findings regarding which cognitive domains are more likely to be impaired varied across studies. Multiple studies found that aspects of executive function and memory were more likely to be impaired [22,25,28], whilst most studies identified global deficits across aspects of various cognitive domains. Findings also varied regarding which aspects of memory are more likely to be impaired; Alwan et al. [25] found that non-verbal memory is more likely to be selectively impaired, whilst Hannan et al. [28] found that subtests related to verbal memory were more likely to identify impairment.

Self-reported measures of cognitive performance

4/14 studies administered only self-reported questionnaires exploring participants' perceived cognitive performance. Two studies [26,27] administered the brief German 'Fragebogen zur geistigen Leistungsfähigkeit' (FLei; [41]) mental ability questionnaire, which assesses self-reported memory, attention and executive function. Participants with TTP rated themselves significantly poorer on all domains compared to healthy controls, and self-rated cognitive performance negatively correlated with results of a self-reported measure of depression (Inventory of Depressive Symptomatology – Self-Report; [42]). However, Falter et al. [26] note that the participants' scores on the FLei were significantly better than depressed individuals' scores in other non-TTP studies.

Holmes et al. [29] administered the Patient-reported Outcomes Measurement Information System Cognitive Function Abilities Subset – Short Form 6a (PROMIS CFAS – SF6a; [43], a brief survey in which participants rate their performance on items related to memory, thinking and concentration. The researchers found that, on average, participants' ratings were at least one SD below US population norms. Mulas et al. [30] administered the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog; [44]), analysing its correlation with other self-reported quality of life measures; participants' perceived cognitive performance positively correlated with reported health-related quality of life. Additionally, Chaturvedi et al. [22] administered the PROMIS Cognitive Function Form 8a [45], a brief screening tool, finding that self-rated cognitive functioning positively correlated with cognitive performance as measured by the NIH Toolbox in their sample.

Correlates of cognitive performance

Where findings were considered in relation to the number of acute TTP episodes and duration since the most recent acute episode, researchers found that these factors do not appear to be correlated with cognitive performance on clinician-administered measures [19,20] or on self-reported measures [26]. Moreover, neurological involvement at time of acute TTP episode (e.g. coma, seizure) does not appear to be a strong predictor of cognitive performance on clinician-administered measures [20,31], but perceived cognitive performance did correlate with neurological comorbidities at time of diagnosis [30]. Where reported, ADAMTS13 levels are also not a predictor of cognitive performance [19,24,31]. However, Boothby et al. [24] identified a significant correlation between CD141 serum levels and lower RBANS scores (indicating poorer performance) in their sample, a possible relationship that was not analysed in any other study.

4/14 studies [22,23,25,28] completed neuroimaging as part of their evaluations. Cerebral findings were associated with cognitive performance in TTP; Alwan et al. [25] found that participants with abnormal

magnetic resonance imaging (MRI) findings had lower P-IQ and V-IQ scores. Hannan et al. [28] reported that pathological changes in the cingulate cortex, frontal, parietal and temporal lobes were correlated with impaired cognitive scores in the domains of concentration, short-term memory and verbal memory. Chaturvedi et al. [22] found that silent cerebral infarction (SCI) was strongly associated with cognitive impairment (both major and minor impairment). Individuals with a history of both SCI and stroke were possibly more likely to exhibit cognitive impairment, though valid statistical analysis was not possible due to small participant numbers. In a follow-up assessment completed after one year, Yu et al. [23] found that cognitive function did not significantly change for the overall sample. However, for people with TTP who did *not* present with SCI progression, cognitive scores improved significantly, demonstrating an association between SCI and cognitive impairment in TTP.

Additionally, Chaturvedi et al. [22] found that scores on the Beck Depression Inventory (BDI-II; [46]) were significantly associated with cognitive impairment when adjusted for SCI and stroke history. However, Selvakumar et al. [32] found that BDI-II scores did not differ significantly between participants with and without cognitive impairment. It is thus difficult to ascertain from existing evidence how much poor mental health may contribute to cognitive deficits seen in TTP, or indeed if treating underlying mental health difficulties may influence cognitive performance.

Discussion

This rapid review describes the existing evidence base regarding the neuropsychological consequences of TTP, identifying 14 articles eligible for inclusion. Most studies had small sample sizes that may have rendered some statistical analyses underpowered, and control groups were rarely utilized. The generalizability of results should thus be interpreted with caution. Overall, TTP was associated with deficits across various cognitive domains, regardless of frequency or severity of acute episodes. Abnormal MRI findings such as SCI, but not ADAMTS13 levels, were associated with cognitive impairment. The association between neurological involvement and cognitive impairment is less certain, but the current literature suggests any correlation may be weak. The potential impact of anti-vWF therapy on cognitive changes in TTP also remains an open question.

Understanding the causal impact of TTP on cognition can be challenging as clinicians usually need to rely on estimates of premorbid intelligence, which was rarely assessed in the literature. However, where this was completed [20,25], it is clear that TTP was associated with neuropsychological consequences. Of particular interest is the question of determining who may benefit from comprehensive neuropsychological assessment. At least one study [25] completed a full cognitive assessment only for participants who self-reported cognitive concerns, whilst most of the remaining studies did not fully detail the recruitment process or specify any mitigating measures taken to ensure that self-selection bias did not affect the overall findings. Moreover, recruitment pools overlapped across some studies (e.g. recruitment via the Oklahoma TTP-HUS Registry or Johns Hopkins University) and it is unclear how frequently participant repetition occurred. Estimating the exact prevalence of cognitive impairment in TTP is thus a challenge, however, the literature is clear that not all survivors of TTP exhibit cognitive deficits or neuropsychological impact.

Several studies utilized brief screening measures (MMSE, MoCA) or brief self-rated surveys (FLei, PROMIS forms), but the predictive value of these measures in identifying objective cognitive impairment remains unclear. Kennedy et al. [20] found that participants' MMSE scores were normal despite presenting with meaningful cognitive impairment, indicating that the MMSE may lack sensitivity in identifying TTP-related deficits. However, the researchers excluded individuals who scored less than 24 on the MMSE as the purpose of the study was to identify impairment in survivors who are 'functionally independent'. This means that individuals who might have experienced major cognitive impairment following TTP, alongside corresponding low MMSE scores, may have been excluded from the cognitive assessment, making it difficult to draw conclusions regarding whether the MMSE may be useful in detecting major cognitive impairment following TTP.

MoCA administration and results were reported by Han et al. [19], although no sensitivity analysis was reported, and the measure has not been specifically validated for use in populations with TTP. The researchers reported an average MoCA score for participants with TTP that differed significantly from population norms but was only just below the commonly recommended cutoff of <26. A recent systematic review

and meta-analysis found that cutoffs of <23 to <25 may provide optimal sensitivity and specificity in identifying mild cognitive impairment [47]. Using these cutoffs, TTP survivors presenting with deficits on neuropsychological measures may have been considered to have normal MoCA scores. Moreover, research has highlighted frequent misclassification of Black individuals when using the MoCA due to a lack of racially stratified norms [48]. Given the over-representation of Black people in TTP [5,6], MoCA scores should thus be evaluated with caution and with particular consideration for demographic details that may factor into the interpretation of obtained scores.

People with TTP describe various ways in which cognitive impairment can affect their quality of life, including a significant impact on relationships with loved ones [49]. Little is known, however, about the impact of TTP on social cognition, a domain categorized in the DSM-5 as playing an important role in emotion recognition and mentalization [16]. No study specifically assessed social cognition in participants, meaning it is the only cognitive domain listed in the DSM-5 that has not been explored in the literature reviewed. Given the prevalence of depression, anxiety and post-traumatic stress disorder in populations with TTP [50], identifying unique neuropsychological properties of social cognitive impairment – and indeed any other cognitive impairment – may pose a challenge. Thorough assessment of mental health, and offering suitable interventions as appropriate, is thus crucial to ensuring that any secondary impact on cognitive health is alleviated.

Implications for clinical practice

Where appropriate, people with TTP may benefit from a comprehensive neuropsychological assessment that encompasses the different cognitive domains, providing them with recommendations on how to manage any identified concerns that can be reassessed and readdressed with them over time. Considering an individual's broader mental health, quality of life, medical history and premorbid functioning is important when drawing any conclusions about the possible causal impact of TTP on cognition.

Caution regarding the reliance on brief screening measures is advised; the sensitivity and specificity of any brief measures in detecting TTP-related neuropsychological consequences are unclear, and it is possible that cognitive deficits may be missed if brief screening measures are the only utilized tool. Additionally, stratified norms related to demographic information (e.g. race) should be considered when interpreting an individual's scores. Clinical judgement, informed by the evidence from the literature, is essential in selecting the appropriate assessment tools, which can contribute to the wider formulation of an individual's difficulties.

Whilst there are possible correlates to cognitive impairment in TTP, it is important not to draw firm conclusions from assumptions or underpowered findings from the literature. For example, survivors of TTP with abnormal MRI findings are more likely to experience cognitive deficits, but it is clear that this is not always the case. Factors such as severity and frequency of acute TTP episodes, serum ADAMTS13 levels and neurological abnormalities should not be relied on to determine who may benefit from comprehensive assessment. The value of self-reported measures in determining who may benefit from further cognitive assessment is currently unclear, and caution is advised in reliance on self-report measures until further research has been undertaken.

Strengths and limitations

There are some notable strengths to this review, the first systematic search of the published literature on the measurement of neuropsychological consequences of TTP. The aim of this review was to capture, consider and present relevant information that can inform clinical practice in TTP, and to highlight important considerations for practitioners who evaluate cognition in this group. Our review is limited by the fact it is a rapid review which considered a relatively narrow focus of research in a shorter timescale. It is thus possible that some articles of interest, including qualitative studies and unpublished results, may not have been captured by the search's parameters. The available timescale – combined with the heterogeneity of the identified studies – also precluded a meta-analysis from being completed.

Recommendations for future research

More high-quality research is needed to understand the impact of TTP on social cognition, as well as the extent of changes in cognition over time in TTP. Importantly, any possible benefits to anti-vWF therapy

on the cognitive impact of TTP (or on factors associated with cognitive impairment, such as SCI) have not been thoroughly evaluated, with just one study [21] exploring this in any depth. Further research in establishing the sensitivity and specificity of brief screening and self-reported measures in identifying TTP-related cognitive impairment would also be particularly valuable for clinicians' decision-making, as well as adequately powered studies to determine possible predictors of cognitive performance in TTP. Finally, research on the possible impact of psychological treatment (e.g. for depression/anxiety) and/or management of SCI risk factors on cognitive performance could provide further context on the relationship between psychological, neurological and neuropsychological health in this population.

Conclusion

In summary, this rapid literature review has outlined the existing evidence base on the measurement of cognition in TTP using clinician-administered or self-reported measures. TTP is associated with cognitive change that can have a real-world impact on the lives of patients, and comprehensive assessment can identify areas in which appropriate advice and support can be provided to help improve individuals' quality of life.

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Author contributions

CRediT: **Seraj Brugi:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing; **Eliane Young:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

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