Systematic review and meta analysis

Cognitive dysfunction and associated neuroimaging biomarkers in antiphospholipid syndrome: a systematic review

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Abstract

Objectives. Cognitive dysfunction is common in patients with aPL (including primary APS or APS associated with SLE). Neuroimaging biomarkers may contribute to our understanding of mechanisms of cognitive dysfunction in these cohorts. This review aimed to investigate: (i) the prevalence of cognitive dysfunction in studies including neuroimaging biomarkers; and (ii) associations between cognition and neuroimaging biomarkers in patients with APS/aPL.

Methods. We conducted a systematic search of electronic databases PubMed, Science Direct, Scopus and PsycINFO, and included studies with descriptions of neuroimaging findings, cognitive dysfunction or both, in patients with aPL positivity (LA, IgG and IgM aCL and anti-β2 glycoprotein-I antibodies).

Results. Of 120 search results we included 20 eligible studies (6 APS, 4 SLE with APS/aPL and 10 NPSLE). We identified a medium risk of bias in 6/11 (54%) of cohort studies and 44% of case–control studies, as well as marked heterogeneity in cognitive assessment batteries, APS and aPL definitions, and neuroimaging modalities and protocols. The prevalence of cognitive dysfunction ranged between 11 and 60.5%. Structural MRI was the most common imaging modality, reporting cognitive dysfunction to be associated with white matter hyperintensities, ischaemic lesions and cortical atrophy (four with cerebral atrophy, two with white matter hyperintensities and two with cerebral infarcts).

Conclusion. Our findings confirm that cognitive impairment is commonly found in patients with aPL (including APS, SLE and NPSLE). The risk of bias, and heterogeneity in the cognitive and neuroimaging biomarkers reported does not allow for definitive conclusions.

Key words: antiphospholipid syndrome, antiphospholipid antibodies, cognitive dysfunction, neuroimaging biomarkers, assessment

Rheumatology key messages

- Limited reporting of cognitive dysfunction in APS compared with SLE and NPSLE with aPL positivity.
- Studies including neuroimaging biomarkers in APS/aPL-positive patients with cognitive dysfunction were scarce and heterogeneous.
- Multicentre studies with standardized image acquisition and international APS clinical and laboratory criteria are required.

Introduction

APS is an autoimmune antibody-mediated disease, characterized by recurrent vascular thrombosis (venous, arterial and microvascular), pregnancy morbidity and thrombocytopenia [1–3]. A characteristic indicator of APS is the presence of aPL, including LA, as well as IgG and IgM aCL, and anti-β2 glycoprotein-I antibodies.
(anti-β2GPI) [2, 4, 5], and diagnosis is made in accordance with the International updated Sapporo (Sydney) classification criteria [6]. APS can occur in isolation, where the disease is classified as occurring alone [primary APS (PAPS)], or in the context of other autoimmune conditions [secondary APS (SAPS)], most notably SLE [7].

Cognitive dysfunction is a common neurological manifestation of APS, particularly in SAPS associated with SLE. Evidence regarding the prevalence of cognitive dysfunction and PAPS is limited [8]. One review reported frequency of cognitive dysfunction to range between 15–80% in cohorts of aPL carriers, PAPS and SLE [9]. The association of cognitive dysfunction with APS has mainly been discussed in the context of NPSLE [10], which according to the ACR consists of 19 neurologic syndromes of the central, peripheral and autonomic nervous systems including cognitive dysfunction or psychiatric syndromes, where other causes have been excluded [11]. Using the ACR consensus criteria, the prevalence of cognitive dysfunction for SLE was reported as 43, 30 and 6% for mild, moderate and severe disease, respectively [12]. Cognitive dysfunction is also common in SLE where there are no neuropsychiatric symptoms [13].

Although neuroimaging biomarkers are a potentially powerful way to understand mechanisms of cognitive impairment, evidence summarizing neuroimaging characteristics of APS is also scarce [2, 14]. One review article described the relationship between cognitive dysfunction and magnetic resonance abnormalities (MRI) specific to patients with SLE [8]. More recently, there has been increasing interest in examining the associations between SLE and aPL with dementia [15, 16].

Given the limited evidence regarding the prevalence and mechanisms of cognitive dysfunction in patients with a diagnosis of APS or aPL positivity, there remains scope to examine available studies reporting detailed cognitive assessment and neuroimaging biomarkers. The objectives of this systematic review were to determine: (i) the prevalence of cognitive dysfunction in studies including neuroimaging biomarkers; and (ii) associations between cognition and neuroimaging biomarkers in patients with APS/aPL.

Methods

Literature search and selection strategy

We electronically searched PubMed, Science Direct, Scopus and PsycINFO up to January 2021 using key terms ‘antiphospholipid syndrome’, ‘neuroimaging’, ‘cognitive impairment’ and ‘neuropsychiatric systemic lupus erythematosus [NPSLE]’, combined using Boolean operators (supplementary Table S1, available at Rheumatology online). In addition to the database searches, reference lists of selected articles were checked for their included relevant research papers.

Publication selection criteria

Publication inclusion criteria were: adult cohorts ≥18 years of age; studies including patients defined as diagnosed with APS (PAPS and SAPS); cohorts with aPL (various combinations of LA, aCL, anti-β2GPI) positivity; and studies reporting both cognitive assessment and neuroimaging biomarkers. Exclusion criteria were: animal studies; paediatric cohort studies; review articles and reports; case reports and case studies (fewer than five subjects); editorials; letters; and commentaries. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17] for the search strategy, study selection and inclusion, as well as data extraction and analysis (see Fig. 1) (supplementary Table S2, available at Rheumatology online).

Quality assessment

We appraised the quality of included studies using the Newcastle-Ottawa Quality Assessment Scale (NOS) for case–control and longitudinal cohort studies [18] and adapted version for cross-sectional cohort studies [19]. The NOS allocates a maximum score of 9 points indicating very high quality and a low risk of bias, whereas a minimum score of 1, 2 or 3 indicates low quality and a high risk of bias. The scoring system allocates up to 4 points for selection of subjects, 2 points for comparability and 3 points for exposure (in case–control cohort studies) and outcome (in cohort studies). Studies scoring above the median value were considered high quality (low risk of bias) and those below the median as low quality (high risk of bias).

Data extraction

For each study we extracted data on: first author and year (study ID); study design; number of patients and controls (if included); mean age in years; percentage female; types and isotypes of aPL and cut-off values; cognitive dysfunction prevalence, cognitive domains assessed; neuroimaging modality and neuroimaging biomarkers assessed; cognitive domains affected; and associations between neuroimaging biomarkers, cognitive dysfunction and aPL positivity.

Results

Search results and publication selection

We identified 120 articles through the electronic search. A detailed search strategy is presented in Fig. 1. Two independent raters (C.D. and D.J.W.) evaluated the studies at the eligibility and inclusion phases of the review where there was full agreement for publication selection.

Quality assessment results for selected studies

Quality assessments of the included studies were undertaken by C.D. using the NOS criteria for cohort and case–control studies are shown in Tables 1 and 2. The median score of NOS was 6 for cohort studies and 7 for case–control studies. Among the 11 cohort studies, 7
were considered of medium to higher methodological quality, scoring ≥6, and for the 9 case–control studies, 5 were considered of medium to higher methodological quality, scoring ≥7. Overall, there were 8 included studies considered of lower methodological quality, and therefore a higher risk of bias in 6/11 (54%) of cohort studies and in 4/9 (44%) of case–control studies.

**Characteristics of studies included in review**

Of the 20 studies included, the disease groups were \( n = 6 \) APS (mixed PAPS and SAPS), \( n = 4 \) SLE specific and \( n = 10 \) NPSLE (see Tables 3 and 4). More than half of the included studies were cohort studies and \( n = 9 \) were case–control (\( n = 2 \) APS/aPL positive, \( n = 3 \) SLE, \( n = 4 \) NPSLE) [20–29]. Three studies were longitudinal in design [30, 31, 23] and at least seven studies were reported as retrospective where patient cohorts and data were extracted from case notes and patient-held registries [32, 33, 34, 35, 36, 27, 28]. Cohort sizes within studies were generally small with the exception of the two most recent included studies [30, 37], with mean age ranging from 31 to 81 years, and >75% were female.
| Quality assessment                                      | APS studies | SLE studies | NPSLE studies |
|--------------------------------------------------------|-------------|-------------|---------------|
|                                                        | Arvanitakis et al. [20] | Homayoon et al. [21] | Zampronni et al. [22] | Erkan et al. [2019] | Chapman et al. [2010] | Whitelaw et al. [1999] | Sarbu et al. [2015] | Steup-Beekman et al. [2013] | Abda et al. [2013] | Zirkzee et al. [2012] | Cantú-Brito et al. [2010] |
| Selection                                               | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 1. Is the case definition adequate                      | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 2. Representativeness of cases                          | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 3. Ascertainment of exposure                            | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 4. Outcome of interest was not present at start of study| ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| Comparability                                           | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 5. Study controls for most important factor             | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 6. Study controls for second important factor           | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| Outcome                                                | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 7. Assessment of outcome                                | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 8. Statistical test (CS only)                           | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 9. Adequate follow up period for outcome of interest (LS only) | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| 10. Adequacy of follow up of cohorts (LS only)          | ●           | ●           | ●             | ●               | ○            | ○             | ●            | ●             | ●            | ●            | ●             |
| Total score                                             | 9/9         | 9/9         | 6/9           | 7/9             | 4/9          | 5/9          | 9/9         | 5/9          | 6/9         | 5/9         | 6/9         |

CS: cross-sectional studies; LS: longitudinal studies.
| Quality assessment | APS studies | SLE studies | NPSLE studies |
|--------------------|-------------|-------------|---------------|
|                     | Tektonidou et al. (2006) [31] | Kozora et al. (2014, 2016) [32],[33] | Appenzeller et al. (2007) [34] |
|                     | Tomietto et al. (2007) [35] | Shulman et al. (2017) [36] | Emmer et al. (2008) [37] |
|                     | Cho et al. (2007) [38] | Roldan et al. (2006) [39] | Appenzeller et al. (2005) [40] |
| Selection           | 1. Is the case definition adequate | ● | ● | ● |
|                     | 2. Representativeness of the cases | ● | ● | ● |
|                     | 3. Selection of controls | ● | ● | ● |
|                     | 4. Definition of controls | ○ | ○ | ● |
| Comparability       | 5. Study controls for most important factor | ● | ● | ○ |
|                     | 6. Study controls for second important factor | ● | ● | ● |
| Exposure            | 7. Measurement method of variables of interest described | ● | ● | ● |
|                     | 8. Methods of measurements same for cases and controls | ● | ● | ● |
|                     | 9. Non-response rate | ○ | ○ | ○ |
| Total score         | 7/9 | 7/9 | 8/9 | 8/9 | 6/9 | 6/9 | 5/9 | 5/9 | 9/9 |
| Author and year | Study design | Sample (n) | Mean age (years) | % Female | aPL+ | aPL types (iso-types; cut-offs) | Cognitive dysfunction | Cognitive domains | Imaging biomarkers | Imaging modality |
|----------------|--------------|------------|------------------|----------|------|--------------------------------|---------------------|------------------|-------------------|-----------------|
| Arvanitakis et al. (2019) | Longitudinal cohort | 956 | 81.1 | 72 | 197 (21) | aCL anti-β2GPI (IgG/M) | Cognitive dysfunction | Global, perceptual memory, episodic memory, semantic memory, visuospatial memory | MRI, TCD | MRI | WMH total volume, lacunes, hippocampus volume, presence of RLS |
| Homayoon et al. (2014) | Cross-sectional, prospective cohort | 1895 | 58 | 70 | 118 (6) | aCL (IgG > 21 U/ml, IgM > 12 U/ml) | MRI WMH, silent cortical infarcts, lacunes, hippocampus volume, presence of RLS | Global | MRI | WM changes |
| Zamproni et al. (2013) | Cross-sectional, observation cohort | 27 | 41 (non-RLS), 35 (RLS) | 70 | 27 (100) | aCL (IgG > 40 GPL); LA (INR > 1, or 3 on AC Rx) | Global, learning memory, visuospatial, nonverbal memory and fluency, executive function, attention, frontal function | TCD | MRI | Presence of RLS |
| Erkan et al. (2010) | Cross-sectional, retrospective cohort | 143 | NR | 88 | 143 (100) | LA; aCL, anti-β2GPI (IgG/M/A) | MRI WM changes | Global learning memory, visuospatial, immediate word span, learning, retrieval efficiency, visuospatial, psychomotor speed, abstract reasoning, conceptual flexibility | MRI, TCD | MRI | Global, attention, immediate word span, learning, retrieval efficiency, visuospatial, psychomotor speed, abstract reasoning, conceptual flexibility |
| Chapman et al. (2008) | Cross-sectional, case-control | 60 (cases), 60 (controls) | 41.1 (cases) | 77 | 60 (100) | aCL (10–20 (elevated), > 20 (high) GPL) | MRI, CT, EEG | Global, dementia criteria | MRI, CT, EEG | Global, dementia criteria | MRI, CT, EEG |

Table 3: Characteristics of studies describing APS (n = 6) and SLE (n = 4) specific studies
| Author and year | Study design | Sample (n) | Mean age (years) | % Female | aPL+ | aPL types (iso - % Cognitive dysfunction types; cut-offs) | Cognitive domains | Imaging modality | Imaging biomarkers |
|-----------------|-------------|------------|------------------|----------|-----|----------------------------------|------------------|-----------------|------------------|
| **SLE-specific studies (n = 4)** | | | | | | | | | |
| Kozora et al. (2014, 2016) | Cross-sectional, 20 (SLE), 20 (aPL+), 10 (control) | 36.5 (SLE), 37.6 (aPL+), 40.8 (control) | All | 20 (50) | LA; aCL, anti-b2GPI (IgG/M) | Global, learning, memory, attention, working memory, executive function, verbal fluency, visuocostructive, motor functioning | MRI, fMRI | WMH, cerebral atrophy |
| Appenzeller et al. (2007) | Longitudinal case-control | 75 (cases), 44 (controls) | 32.3 (cases), 33.8 (controls) | 28 (37) | NR | Global, simple/complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, executive function | MRI | Cerebral atrophy |
| Tomietto et al. (2007) | Cross-sectional, prospective case-control | 52 (SLE), 20 (RA) | 36.3 (SLE), 41 (RA) | 35 (67) | LA (aPTT); aCL (<15 IgG IU/ml) anti-b2GPI (<20 IgG IU/ml) | Global, simple/complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, executive function | MRI | Cortical atrophy, focal lesions |
| Whitelaw et al. (1999) | Cross-sectional, 69 prospective cohort | 34.0 | 97 | 16 (23) | aPL (IgG) | Intelligence, logical memory, visual reproduction, learning, executive function, auditory verbal learning | MRI | Diffuse and focal ischaemic change, WM lesions, UBOs |

1 Same cohort in both publications. AC: anticoagulants; anti-b2GPI: anti-b2 glycoprotein-I antibodies; CA: cornu ammonis; EEG: electroencephalogram; fMRI: functional MRI; INR: international normalized ratio; NR: not reported; PAPS: primary APS; RLS: right to left shunt; Rx: treatment; SAPS: secondary APS; TCD: transcranial Doppler; UBOs: unidentified bright objects; WM: white matter; WMH: white matter hyperintensities; WML: white matter lesions.
### Table 4 Characteristics of studies describing NPSLE ($n = 10$) specific cohort studies

| Author and year | Study design  | ($n$) sample | Mean age (years) | % Female | aPL+   | APS   | NPSLE | LA; aCL, anti-2GPI (IgG/M) | % Cognitive dysfunction | Cognitive domains | Imaging modality | Imaging biomarkers |
|-----------------|---------------|--------------|------------------|----------|--------|-------|-------|-----------------------------|-----------------------|------------------|-----------------|------------------|
| **NPSLE studies ($n = 10$)** |               |              |                  |          |        |       |       |                             |                       |                  |                 |                  |
| Shulman et al. (2017) [36] | Cross-sectional, case–control | 21 (cases), 11 (controls) | 40.14 (cases), 39.6 (controls) | NR       | 2 (10) | 4 (19) | 14 (67) | Global, memory, information processing speed, executive function, visual spatial, verbal function, motor skills, problem solving, attention | 47.6 | Global, memory, information processing speed, executive function, visual spatial, verbal function, motor skills, problem solving, attention | MRI, OCT | Infarcts, UBOs, retinal nerve fiber layer thickness (biomarker for white matter damage) |
| Sarbu et al. (2015) [26] | Cross-sectional, retrospective cohort | 108 | 40.6 | 92 | 37 (34) | LA; aCL (IgG/M) | 11 | Global, simple/complex at-MRI attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, executive function | WMH, infarcts, atrophy | WMH, infarcts, atrophy | MRI, LVD, SVD |
| Steup-Beekman et al. (2013) [37] | Cross-sectional, retrospective cohort | 155 | 29.7 (median) | 90 | 104 (67) | LA; aCL (IgG/M) | 25.6 | Global, simple/complex at-MRI attention, memory, visuo-spatial processing, language, reasoning/problem solving, psychomotor speed, executive function | WMH, infarcts, atrophy | WMH, infarcts, atrophy | MRI, LVD, SVD |
| Abda et al. (2013) [28] | Cross-sectional, prospective cohort | 34 | 33.2 | 94 | 12 (35) | aPL | 42.86 | Global, attention, memory, MRI, DWI, problem solving, visuo-spatial processing, psychomotor speed | MRI, MRA | Global, attention, memory, MRI, DWI, problem solving, visuo-spatial processing, psychomotor speed | MRA | Ischaemic brain lesions and demyelination, infarctions, diffuse brain atrophy |
| Zirkzee et al. (2012) [29] | Cross-sectional, retrospective cohort | 71 (SLE) | 42 | 90 | 48 (68) | LA; aCL | 60.5 | Global intelligence, memory, executive function, psychomotor speed | MRI, OCT | Global intelligence, memory, executive function, psychomotor speed | Infarction, inflammation |
| Cantú-Brito et al. (2010) [30] | Longitudinal, prospective cohort | 109 | 34 | 95 | 17 (16) | aCL (IgG) | 38.5 | Memory, language, calculation, construction, reasoning | TCD | Memory, language, calculation, construction, reasoning | Microembolic signals—vascular damage |
| Emmer et al. (2008) [37] | Cross-sectional, prospective case–control | 52 | 38.5 (cases), 44.7 (controls) | 38 (73) | 38 (73) | aCL (IgG/M) | 13.5 | NR | MTI, MRS | Histogram peak height, NAA:Cr ratio | (continued) | (continued) | (continued) | (continued) |

(continued)
| Author and year | Study design | (n) sample | Mean age (years) | % Female | aPL+ | aPL types (iso-types; cut-offs) | % Cognitive dysfunction | Cognitive domains | Imaging modality | Imaging biomarkers |
|----------------|--------------|------------|------------------|----------|------|---------------------------------|----------------------|-----------------|----------------|------------------|
| Cho et al. (2007) [38] | Cross-sectional, retrospective case–control | 25 (NPSLE), 18 (NBD) | 31 (NPSLE), 38 67 (NBD) | 13 (30) | 13 (30) | aCL, anti-β2GPI | 25.5 | NR | MRI | WMH, infarcts, parenchymal haemorrhage, atrophy, abnormal intracranial and meningeal enhancement |
| Roldan et al. (2006) [39] | Cross-sectional, retrospective case–control | 28 (SLE), 28 (controls) | 40 (SLE), 37 82 (controls) | 19 (68) | 19 (68) | LA; aCL; aPL (IgG/M/A) | 57 | NR | MRI | Infarcts, periventricular and WMH, cortical atrophy, ventricular dilation |
| Appenzeller et al. (2005) [40] | Cross-sectional, prospective case–control | 115 (SLE), 44 (controls) | 33.5 (cases), 33.8 (controls) | 32 (28) | 32 (28) | LA; aCL (IgG/M) | 30 | Global, simple/complex at-MRI | Cerebral atrophy, infarcts |

Anti-β2GPI: anti-β2 glycoprotein-I antibody; Cr: creatinine; DWI: diffusion-weighted imaging; LVD: large vessel disease; MRA: magnetic resonance angiography; MRS: magnetic resonance spectroscopy; MTI: magnetization transfer imaging; NAA: N-acetylaspartate; NBD: neuroBehcet’s disease; NR: not reported; OCT: optical coherence tomography; SVD: small vessel disease; TCD: transcranial Doppler; UBOs: unidentified bright objects; WMH: white matter hyperintensities.
| Author and year                                      | Sample (n) | Cognitive domain(s) affected | Statistical analysis | Cognitive dysfunction (exposure) and imaging biomarkers (outcome) | Imaging biomarkers (exposure) and aPL+ (outcome) | Cognitive dysfunction (exposure) and aPL+ (outcome) |
|----------------------------------------------------|------------|------------------------------|----------------------|-----------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Structural MRI (n = 16)                            | 956        | No specific domains reported | Linear regression    | Association not assessed                                        | Presence of brain infarcts and aPL+ (OR 1.007, P = 0.97) | Global cognitive function and aPL+ (beta = -0.062, P = 0.203) |
| Arvanitakis et al. (2019) [20]                     | 1895       | No specific domains reported | Linear regression    | Association not assessed                                        | Hippocampal volume and aCL (IgG) (beta = -0.071, CI 0.013, 0.007, P = 0.003) | Global cognition and aCL status (beta = -0.361, CI 0.166, 0.058, P = 0.020); aCL (IgG) (beta = -0.591, CI 1.058, 0.124, P = 0.01) |
| Homayoon et al. (2014) [21]                        | 143        | No specific domains reported | \( \chi^2 \) statistic (Fisher’s exact test) | Association not assessed                                        | WM changes and high titer aCL (RR 2.03, CI 1.04, 3.94, P = 0.02) | Cognitive dysfunction and high titer aCL (P = 0.12) |
| Erkan et al. (2010) [23]                           | 60 (cases), 60 (controls) | Complex attention and verbal fluency | Logistic regression  | Cognitive deficits and; WMLs (OR 4.18, CI 1.33, 13.11, P = 0.01); infarcts (OR 1.22, CI 0.35, 4.20, P = 0.76) | Cognitive deficits and; aCL (IgG) (OR 1.92, CI 0.34, 10.78, P = 0.46); aCL (IgM) (OR 0.63, CI 0.22, 1.78, P = 0.38); LA (OR 2.38, CI 0.76, 7.40, P = 0.14); anti-\( \beta_2 \)GPI (OR 2.11, CI 0.74, 6.05, P = 0.16) | Cognitive impairment and aPL+ (P > 0.232) |
| Tektonidou et al. (2006) [31]                      | 20 (SLE), 20 (aPL+) | Highest frequency of impairment in visual learning and memory, visuomotor speed and flexibility, verbal fluency, visuomotor construction and rapid auditory information processing | Spearman’s correlation | Cognitive impairment and abnormal/incidental MRI findings (P = 0.75) | Association not assessed | Cognitive defect and high titer aCL (P = 0.12) |
| Kozora et al. (2014) [32]                          | 75 (cases), 44 (controls) | General memory                | t-statistic [SPM]     | Severe cognitive dysfunction and reduced WM and GM (statistical result not reported) | Reduced WM and GM and aPL+ (statistical result not reported) | Association not assessed |
| Appenzeller et al. (2007) [34]                     | 115 (cases), 44 (controls) | No specific domains significant | Linear regression    | Cognitive dysfunction and reduced corpus callosum and cerebral volumes (P = 0.001) | Cerebral and corpus callosum volumes and aPL+ (P = 0.1) | Cerebral and corpus callosum volumes and aPL+ (P = 0.1) |
| Tomietto et al. (2007) [35]                        | 52 (SLE), 20 (RA) | Memory, complex attention and executive function | Logistic regression  | Severity of cognitive deficits and MRI severity (cerebral atrophy and ischaemic lesions) (OR 4.9, CI 1.2, 20.3, P = 0.03) | MRI severity (cerebral atrophy and ischaemic lesions) (OR 7.9, CI 1.5, 20.3, P = 0.03) | MRI severity (cerebral atrophy and ischaemic lesions) (OR 4.9, CI 1.2, 20.3, P = 0.03) |

(continued)
| Author and year            | Sample (n) | Cognitive domain(s) affected                                                                 | Statistical analysis             | Cognitive dysfunction (exposure) and imaging biomarkers (outcome)                                                                 | Imaging biomarkers (exposure) and aPL+ (outcome) | Cognitive dysfunction (exposure) and aPL+ (outcome) |
|---------------------------|------------|---------------------------------------------------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Whitelaw et al. (1999) [25] | 69         | Intelligence, visual reproduction, learning, executive function, auditory verbal learning      | Pearson’s correlation,           | Cognitive dysfunction and WMH (P = 0.045)                                                                                       | VBRs and aPL+ (r = -1.01, P = 0.0004)             | Executive function (OR 4.1, P = 0.01); macroischaemic lesions (OR 33.5, CI 3.23–348.3, P < 0.01) |
| Sarbu et al. (2015) [26]   | 108        | No specific domains reported                                                               | $\chi^2$ statistic (Fisher’s exact test) | Cognitive dysfunction and aPL (P = 0.045)                                                                                       | WMH (P = 0.018); microbleeds (P = 0.002); cortical atrophy (P = 0.008); and LA          | Association not assessed                              |
| Steup-Beekman et al. (2013) [37] | 155    | No specific domains reported                                                               | Descriptive statistics           | Association not assessed                                                                                                       | Association not assessed                                                      | Association not assessed                              |
| Abda et al. (2013) [28]    | 34         | Attention, memory, problem solving, visual-spatial processing, psychomotor speed            | $\chi^2$ statistic (Fisher’s exact test) | No statistical differences cognitive deficits and MRI abnormalities                                                              | Association not assessed                                                      | Association not assessed                              |
| Zirkzee et al. (2012) [29] | 71         | No specific domains reported                                                               | $\chi^2$ statistic               | Association not assessed                                                                                                       | Association not assessed                                                      | Association not assessed                              |
| Emmer et al. (2008) [37]   | 52         | No specific domains reported                                                               | Linear regression                | Cognitive dysfunction and; lower MTR histogram peak for brain parenchyma (beta = -0.435, R = 0.664, P < 0.001); WM (beta = -0.445, R = 0.647, P < 0.001); GM (beta = -0.306, R = 0.663, P < 0.01) | aCL on MTR histogram parameters (ns)                                                      | Association not assessed                              |

(continued)
| Author and year | Sample (n) | Cognitive domain(s) affected | Statistical analysis | Cognitive dysfunction (exposure) and imaging biomarkers (outcome) | Imaging biomarkers (exposure) and aPL+ (outcome) | Cognitive dysfunction (exposure) and aPL+ (outcome) |
|----------------|------------|-------------------------------|----------------------|---------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Cho et al. (2007) [38] | 25 (NPSLE), 18 (NBD) | No specific domains reported | $\chi^2$ statistic | Association not assessed | Association not assessed | n = 3 patients with cognitive dysfunction were aPL+ (assocation not assessed) |
| Roldan et al. (2006) [39] | 28 (SLE), 28 (controls) | No specific domains reported | Fisher's exact test | Association not assessed | Old cerebral infarcts and aPL+ and aCL ($P < 0.001$) | Association not assessed |
| fMRI (n = 1) | 40 (cases), 10 (controls) | Executive function, working memory | Wilcoxon rank-sum test | Higher activation in bilateral frontal, temporal and parietal cortices during working memory and executive function tasks ($P < 0.001$) | Higher activation in bilateral frontal, temporal and parietal cortices and aPL+ ($P < 0.001$) | Higher activation in bilateral frontal, temporal and parietal cortices during working memory and executive function tasks for aPL+ ($P < 0.001$) |
| TCD (n = 2) | 27 | Global cognition and executive function | Mann-Whitney U test | Worse global cognition and executive function with sRLS ($P < 0.05$) | Association not assessed | Association not assessed |
| Cantú-Brito et al. (2010) [30] | 109 | Memory, attention, visuospatial construction | $\chi^2$ statistic, logistic regression | Cognitive dysfunction and MES ($P = 0.036$), cognitive dysfunction and MES (beta = 0.61, $P = 0.19$) | MES and aCL (IgG) (ns) | Association not assessed |
| EEG and CT (n = 1) | 23 | No specific domains reported | Fisher's exact test | Association not assessed | Association not assessed | Association not assessed |
| OCT (n = 1) | 21 (cases), 11 (controls) | No specific domains significant | Pearson correlation | RNFL thickness and global cognition ($r = -0.17, P = 0.45$); memory ($r = 0.08, P = 0.70$); executive function ($r = -0.25, P = 0.26$); attention ($r = 0.14, P = 0.53$); information processing speed ($r = -0.18, P = 0.46$); visual spatial ($r = -0.26, P = 0.26$); verbal function ($r = 0.19, P = 0.42$); motor skills ($r = -0.28, P = 0.21$) | Association not assessed | Association not assessed | Association not assessed |

Anti-β2GPI: anti-β2 glycoprotein-I antibody; beta: coefficient for a multiple linear regression; EEG: electroencephalogram; fMRI: functional MRI; GM: grey matter; MES: microembolic signals; MTR: magnetization transfer ratio; NBD: neuroBehçet’s disease; ns: not statistically significant; OCT: optical coherence tomography; OR: odds ratio; $P$: statistical significance probability; R: correlation between predicted and observed values; RNFL: retinal nerve fiber layer; RR: relative risk ratio; r: Pearson’s correlation; SPM: statistical parametric mapping; sRLS: significant right to left shunt; TCD: transcranial Doppler; VBR: ventriculo brain ratios; WM: white matter; WMH: white matter hyperintensities; WML: white matter lesions. Bold text indicates results statistically significant.
Prevalence and assessment of cognitive dysfunction and/or dementia

The prevalence of cognitive dysfunction for all included studies across all patient groups ranged from 11% [34] to 60.5% [36], although some studies did not report this [30, 37, 39, 23] (see Tables 4 and 5). The prevalence of cognitive dysfunction in APS [mixed—PAPS, SAPS and aPL carriers (+); six studies including 3104 patients] ranged from 15 to 42%. The prevalence of cognitive dysfunction in SLE (4 studies, 236 patients) ranged from 40 to 60%, and in NPSLE (10 studies, 718 patients) from 11 to 47.6%.

Two studies assessed cognition using a global measure such as the Mini-Mental State Examination [37] or the Short Mental Test [33], whereas other studies included global cognition and other detailed neuropsychological batteries [30, 38, 40, 36, 20–23, 25, 29]. Some studies [34, 35, 21–24, 29] reported adherence to the neuropsychological battery for SLE suggested by the ACR and included the cognitive domains global cognition, simple/complex attention, memory, visuospatial processing, language, reasoning/problem solving, psychomotor speed, executive function [11]. There was heterogeneous use of neuropsychological batteries and in turn cognitive domains assessed across studies, except for where there was consistent use of the recommended ACR neuropsychological battery [34, 35, 21, 22, 24, 29]. A limited number of studies report specific cognitive domains affected and for those that did, memory and/or executive function were the most common domains to be identified [38, 39, 40, 22–24], followed by attention [40, 20, 24] (see Table 5). One study [33] examined the association of APS with dementia and included the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [41] criteria for dementia to select the dementia cohort (56%).

APS criteria and aPL assessment

Eight studies included cohorts with APS [38, 32, 35, 31, 20, 25, 26], with three studies inclusive of patients with PAPS [38, 32, 20]; of the five NPSLE studies, <25% of these studies’ cohorts were defined as APS. Only three studies [32, 33, 20] were inclusive of cohorts that were aPL carriers and the frequency of aPL carriers ranged between 6 and 73% in the remaining studies (see Tables 3 and 4). Seven studies adhered to the Sapporo Criteria for inclusion of patients with APS or to indicate presence of aPL positivity at least twice, measured 12 weeks apart. Some studies [35, 31, 20, 27] reported using the original preliminary classification criteria for definite APS [42], whereas others, including some recent studies [38, 32, 21, 22], used the updated Sydney classification criteria [6]. The remaining other 13 studies included patients with aPL positivity and only one of these studies [25] reported that the presence of aPL was recorded at least twice over 12 weeks apart, whereas all other studies [30, 37, 33, 34, 39, 40, 36, 23, 24, 26, 27, 29] recorded the presence of aPL following a single sample and did not specify that aPL was retested to confirm persistence. A small number of studies included all three criteria aPL (LA; IgG and IgM aCL; and anti-β2GPI) [32, 20–22, 24, 25], with the combination aCL and LA as the most common included antibodies [38, 34, 35, 36, 28, 29] or aCL as the only included aPL [37, 33, 31, 26, 27]. Only five studies indicated their cut-off values for aPL [32, 33, 37, 38, 24], with two of these studies using the Sapporo/Sydney laboratory criteria [38, 32]. One study made reference to single, double and triple aPL-positivity and reported these as 3 (15%), 6 (30%) and 11 (55%), respectively [21, 22]. Where aPL methods were specified, the analysis reported referred to the DRVVT and/or APTT and Kaolin clotting time for LA, and the use of ELISA for aCL and anti-β2GPI.

Associations between imaging biomarkers and cognitive dysfunction

For studies inclusive of MRI biomarkers, these reported associations between white matter hyperintensities (WMH) or white matter lesions, ischaemic lesions, cerebral atrophy and cognitive dysfunction [34, 20]. Three studies [23, 24, 29] reported statistically significant associations between cortical atrophy and cognitive dysfunction. Studies including other imaging modalities also reported associations with cognitive dysfunction [38, 31, 26]. Four studies [33, 40, 21, 25] found no association between imaging biomarkers and cognitive dysfunction. Some studies did not examine the association between imaging biomarkers and cognitive function [30, 37, 32, 39, 35, 36, 27, 28] (see Table 5).

Associations between imaging biomarkers and aPL positivity

Two studies [32, 34] found associations between white matter changes and aPL positivity. [24, 28]. Four studies [37, 39, 34, 23] reported associations between cerebral atrophy and aPL positivity [37, 39, 34, 24] while other studies [30, 33, 31, 21, 26, 29] found no association between imaging biomarkers and aPL positivity. Some studies did not examine associations between imaging biomarkers and aPL positivity [38, 33, 35, 36, 40, 20, 25, 27] (see Table 5).

Associations between cognitive dysfunction and aPL positivity

For associations between cognitive dysfunction and aPL positivity, one study reported statistically significant associations for global cognition with positive aCL (participants were classified as aCL positive if the aCL titre (any isotype) was positive in the blood sample) [37]. Other studies found severity of cognitive deficits; executive dysfunction, complex attention, intelligence, visual reproduction, learning (easy) and auditory verbal learning to be associated with aPL positivity (aPL positivity was defined as levels of aCL >15 IgG phospholipid units/ml and levels of anti-β2GPI I IgG >201U/ml) [24], or aPL positivity not defined) [39]. One study reported that in...
aPL-positive patients (defined as a positive LA test; aCL IgG/IgM >40 units; and/or anti-β2GPI IgG/IgM >40 units; on two or more occasions), 45.5% with abnormal MRI findings were cognitively impaired [21], while another study reported 39% of APS patients had cognitive dysfunction and a trend towards higher levels of aPL [aCL 10–20 (elevated), >20 (high) GPL units] in demented APS patients but did not report it as statistically significant [33]. Six studies [30, 32, 33, 20, 21, 27] found no association between cognitive dysfunction and aPL positivity and over half of the included studies [38, 31, 34–36, 40, 23, 25, 26, 28, 29] did not examine this association (see Table 5).

Discussion
In this review, we summarized the literature regarding neuroimaging biomarkers used to identify neuropathology and cognitive dysfunction in APS/aPL-positive patients. Few studies have been inclusive of cognitive function and neuroimaging biomarker data in primary APS patients, and most studies available include SLE and NPSLE cohorts with aPL. There was vast heterogeneity between the 20 observational (case–control and cohort) included studies on various levels, from use of different cognitive assessment batteries, APS and aPL definitions and criteria, to wide variation in neuroimaging modalities. The quality assessment results for half of included studies was of a lower methodological quality, resulting in a higher risk of bias. There were more studies that included NPSLE cohorts in comparison with studies exclusive for PAPS and SAPS, which were all SLE-specific cohorts.

Prevalence and assessment of cognitive dysfunction in APS and aPL-positive patients
The prevalence range of cognitive dysfunction reported for APS and aPL-positive patients was diverse, with half of the studies documenting the rate to be 30% or higher in all APS, SLE and NPSLE cohorts. Similar figures have been previously reported for APS and aPL carriers [9, 43], and even higher rates of cognitive dysfunction for SLE and NPSLE patient cohorts [12]. Although there has been previous reporting of cognitive dysfunction in these patient groups [8, 13], only a limited number of studies, mainly with small sample sizes, have assessed cognitive function using standardized batteries, e.g. the ACR neuropsychological battery [11]. We included only one study that reported prevalence of dementia associated with APS to be 56% [33], which was also reported to be high in previous reviews [16, 44, 45]. It was not evident from the studies reviewed whether factors such as age, gender, education levels and possible cardiovascular risk factors are associated with cognitive dysfunction in APS and aPL carriers, as these variables were rarely controlled for where multivariate analysis was conducted.

Consistent patterns of cognitive dysfunction among the included studies were for specific domains memory, executive function and attention, where reported. This pattern of cognitive domains affected has been previously reported for APS and aPL carriers [9], and executive function for SLE, whereas verbal reasoning and visuo-spatial organization was found to be associated with NPSLE diagnosis [13]. The evidence indicates that patients with APS and/or aPL (including associated autoimmune conditions, i.e. SLE or NPSLE) have some degree of cognitive dysfunction. The clinical presentation in terms of cognitive domains affected is similar to patterns associated with vascular cognitive impairment, including large vessel disease [46], subcortical small vessel disease and dementia [47, 48]. More importantly, none of the studies included in this review or those previously reported has assessed or detected the onset of a diagnosis of mild cognitive impairment. Insidious cognitive decline may be of great benefit to assess clinically for planning treatment interventions and where detected, offer further insight into the neuropathological basis of cognitive dysfunction in APS and aPL carriers.

APS criteria and aPL assessment
This review highlights the dearth of studies available focusing on primary APS and aPL carriers that examine cognitive dysfunction and include neuroimaging biomarker data. We found there was also a limited number of studies that assessed the presence of all three criteria aPL, adhered to the Sapporo Criteria, specified that aPL were persistent, or made reference to single, double and triple aPL-positivity [5]. In order to determine the pattern of cognitive dysfunction, it is important to establish more homogeneous APS and aPL cohorts before extracting meaningful conclusions regarding associated cognitive status. There were also wide variations in technical differences in antibodies quantification, adding further to the heterogeneity issue in the cohorts included. Stricter adherence to the Sydney (update Sapporo) criteria, particularly the laboratory criteria, when selecting cohorts for inclusion in APS and aPL studies [4, 5] would improve generalizability when drawing conclusions from these patients’ groups.

Associations between neuroimaging biomarkers and cognitive dysfunction
As expected, cognitive dysfunction was found to be associated with white matter lesions or WMH, ischaemic lesions and cortical atrophy from studies inclusive of structural MRI. The high burden of WMH in APS patients has been referred to as resembling multi-infarct dementia as a result of vascular damage [49]. In other disease pathologies cognitive decline strongly correlates with cortical atrophy [50], which is also the finding for APS patients in this review indicating degenerative brain changes. The cognitive dysfunction may be explained by the small vessel ischaemic events and also by the underlying pathophysiology as a result of brain volume loss. Most of the studies did not examine or report if there were particular associations between specific
cognitive domains affected and neuroimaging biomarkers’ findings. The only reported magnetization transfer imaging study revealed lower magnetization transfer ratio peak height of brain parenchyma, white matter and grey matter for NPSLE patients compared with healthy controls suggestive of axonal dysfunction and demyelination [26]. The transcranial Doppler studies were also supportive of the association between cognitive dysfunction and vascular damage, with patients that had significant right to left shunt or presence of microembolic signals having worse cognitive function. Although the evidence is targeted at understanding explanations for cognitive dysfunction in APS, the actual rate of cognitive change progression has not been studied despite the potential of neuroimaging biomarkers to detect pathological brain changes from a mild cognitive impairment diagnosis onwards.

Associations between neuroimaging biomarkers and aPL positivity

Significant associations were reported for WMH, cerebral infarcts and cortical atrophy with aPL positivity. WMH, microbleeds and cortical atrophy were associated with LA, and old cerebral infarcts and hippocampal volume loss with aCL. These findings are consistent with neuroimaging studies of patients with APS, in that Zhu et al. [2] found the main characteristics of neurological APS in the brain were ischaemic changes as in multifocal cerebral infarctions, white matter demyelination and cerebral atrophy. Kaichi et al. [14] also found similar MRI abnormalities, including large territorial infarctions, lacunar infarctions in the deep white matter, localized cortical infarctions in the middle cerebral artery territory, bilateral border zone infarctions, anterior basal ganglia lesions and stenotic arterial lesions, all of which were more common in SLE patients with APS. In an earlier review, Sanna et al. [51] also outlined similar brain involvement in aPL-positive patients. However, another recent study reported finding no difference in structural and functional brain connectivity in SLE patients vs controls according to neuropsychiatric involvement or aPL status [52]. Although we reported associations between neuroimaging biomarkers and aPL positivity, it is worth noting that the same number of studies found no association.

Associations between cognitive dysfunction and aPL positivity

Over half of the studies did not examine associations between cognitive dysfunction and aPL, despite inclusion of both variables in each of the studies in addition to neuroimaging biomarkers. Deficits in global cognition were found to be associated with aCL positivity and in terms of deficits in specific cognitive domains, executive dysfunction, complex attention, intelligence, visual reproduction and learning were associated with aPL positivity. The single study that used functional MRI reported higher brain activation in bilateral frontal, temporal and parietal regions during working memory and executive function tasks; the authors explained cortical over-activation as a compensatory mechanism for early white matter neuropathology [22]. There are no other reviews to our knowledge that compare specific cognitive domains affected with aPL positivity. The associations found between neuroimaging biomarkers and cognitive dysfunction are possibly best explained by neuronal impairments through vascular disease, e.g. thrombotic, immune or neuronal effects. There is increasing interest in understanding the pathophysiological process for cognitive dysfunction and APS, and more recent reviews have explored the association between APS and dementia, e.g. aPL and dementia [16] and the evidence between SLE and dementia [15]. Cognitive dysfunction and APS has been mainly explained by hypercoagulability, as aPL are likely to attack vascular endothelial cells, activating the inflammatory response and coagulation cascade, which results in occlusive thrombosis leading to progressive compromise of neural activity and a resulting decline in cognitive function and ultimately vascular dementia [15]. Despite the fact that cognitive dysfunction cannot be explained exclusively by thrombotic events or hypercoagulability, stroke and transient ischaemic attack are the only included neurological manifestations in the 2006 APS criteria [53].

Limitations and other confounders for consideration

Seven of the included studies were retrospective with cohorts selected from referrals (potentially leading to selection bias) or patient registries. Moreover, the duration of disease varied widely across studies and was not controlled for in multivariate analysis. Given the association between cognition and mood, greater inclusion and investigation of depression scales are also warranted in future. Regional or ethnic differences were also not identified in the cohorts included, which adds further to the sampling heterogeneity within APS studies [54]. Other antibodies, either non-criteria aPL or other antibodies, may play a role in the pathogenesis of neural damage and associated brain pathology, and thus also account for cognitive dysfunction in patients with APS, e.g. noncriteria aPL such as anti-phosphatidylserine/prothrombin antibodies, lymphocytotoxic antibodies [55], antirevulamate receptor antibodies [56], brain-derived neurotrophic factor [57], anti-ribosomal P [58] and MMP-9 [59]. Other confounders that may interfere with results reported is the use of medications such as thrombolytic and CS therapies. Correlations between cognition and neuroimaging were inconsistent; indeed, six of the studies included found no correlation. We acknowledge the small sample sizes, which limit the precision of studies reporting correlations between cognitive and brain imaging findings; moreover, heterogeneity of cognitive measures and neuroimaging ratings do not allow definitive conclusions on these complex relationships. In conclusion, multicentre studies in representative populations with standardized image acquisition and protocols, including clearer definitions of the clinical
populations using international clinical and laboratory criteria for APS, are required.

Nevertheless, our findings confirm that cognitive impairment is commonly found in patients with aPL (including those with APS, SLE and NPSLE). The correlations of cognition with neuroimaging biomarkers suggest that neuroimaging studies should be incorporated in research and clinical practice to understand mechanisms of cognitive impairment in patients with aPL. Ultimately, determining and investigating the strength of the association between neuroimaging biomarkers and cognitive impairment in APS/aPL-positive patients could in future guide clinicians in symptomatic or disease-modifying treatment strategies.

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**Data availability statement**

The authors confirm that the data supporting the findings of this review are available within the article.

**Supplementary data**

Supplementary data are available at *Rheumatology* online.

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