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Morphometric MRI findings in patients with suspected autoimmune psychosis spectrum syndromes and association with EEG slowing, CSF changes, and psychometric/neuropsychological findings

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Introduction: Patients with autoimmune encephalitis – who often have accompanying psychiatric symptoms – frequently have electroencephalography (EEG) changes and normal conventional magnetic resonance imaging (MRI) findings. The aim of this paper was to analyze automated EEG and morphometric MRI findings in psychiatric patients with suspected autoimmune psychosis (AP) spectrum syndromes versus controls and the correlation of MRI measures with EEG, cerebrospinal fluid (CSF), and psychometric/neuropsychological findings.

Participants and methods: In total, forty patients were included. Suspected AP spectrum syndromes were defined broadly based on the autoimmune psychiatric syndrome concept. All patients showed signs of an autoimmune process. That is, upon further diagnostic testing, they tested at least positive for well-characterized neuronal antibodies, novel central nervous system antibodies, or well-characterized systemic antibodies with brain involvement. For EEG, thirty-seven matched patient-control pairs, and for structural MRI, thirty-five patients and matched controls, were available. EEG analysis for intermittent rhythmic delta/theta activity (IRDA/IRTA) was performed using independent component analysis. MRI scans were analyzed using FreeSurfer (7.2) for the subcortical measures and CAT12 for cortical thickness and global volumes.

Results: Patients did not show significantly increased IRDA/IRTA rates. Regarding brain volumes, there was a significant decrease in grey matter volume/total intracranial volume (TIV) ($p=0.027$) and a significant increase in CSF/TIV ($p=0.027$), which remained significant after correction for multiple comparisons. Further differences with lower white matter volume/TIV, reduced cortical thickness in the left parahippocampal and transversotemporal gyri and an increase in the volume of the left lateral ventricle of patients did not remain significant after correcting for multiple testing. White blood cell counts in the CSF of the whole patient group correlated positively with increased hippocampal volumes. Brain volumes did not correlate with psychometric scales, but with several neuropsychological scores.

Discussion: Autoantibody-associated suspected AP spectrum syndromes seem to be associated with slight global grey matter volume reductions and secondary increased CSF volumes. Associations between hippocampal volume increases and inflammatory CSF markers could, in contrast, reflect edematous swelling within the limbic system. Further multimodal imaging studies of more homogeneous AP groups might be promising to detect morphometric correlates.

KEYWORDS

autoantibody, neuroinflammation, structural MRI, cortical thickness, brain

Introduction

Autoimmune psychosis (AP) could be interpreted as an oligosymptomatic subtype of autoimmune encephalitis (AE) characterized by a predominantly psychiatric presentation (1–6). AP appears to be the most common psychiatric presentation of AE (2, 5–7). Clinical manifestations might, however, go beyond classical presentations of psychosis (e.g., by manifesting as autoimmune affective, neurocognitive or obsessive-compulsive syndromes) (8–10). Therefore, some authors suggest the term autoimmune psychiatric syndrome or symptoms (APS) (6, 8, 11). Patients with AP are characterized by some specific clinical manifestations, such as acute polymorphic psychotic or catatonic syndromes (2, 7, 12). The diagnostic work-up for AP usually includes a blood test for anti-central-nervous-system (CNS) or rheumatic antibodies, electroencephalography (EEG), magnetic resonance imaging (MRI) of the brain, and cerebrospinal fluid (CSF) analysis, including routine parameters such as white blood cell (WBC) count or oligoclonal bands (OCBs) and anti-CNS antibodies (2, 7, 13, 14). CSF analyses appear to be the most sensitive tests for the detection of AP/APS (9, 10). According to the consensus criteria of Pollak et al. (2), the detection of well-characterized anti-neuronal antibodies of the immunoglobulin G (IgG) type is required for a definite AP diagnosis. In diagnostically ambiguous cases, [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) has emerged as a valuable additional tool (6, 15–25). EEG seems to be a sensitive, albeit non-specific, diagnostic investigation for AE. Patients with NMDA-R AE, the most common form of AE with frequent additional psychotic symptoms (3, 26), show EEG pathologies in 84%–90% of cases (27, 28). In critically ill

NMDA-2R AE patients in intensive care units, a specific EEG signal, the extreme delta brush, has been observed (29). In contrast, conventional MRI examinations are less sensitive and have revealed pathological findings in only approximately 33% of NMDA-R AE cases (27). Other neuronal antibodies, such as GAD65 or LGI1, are frequently associated with T2/FLAIR hyperintensities in the medial temporal lobe (1, 30, 31). Advanced quantitative MRI analyses have demonstrated structural and functional MRI changes, such as hippocampal volume loss, impaired white matter (WM) integrity, and disruption of functional brain networks, even in patients with NMDA-R AE with predominantly normal conventional MRIs (31). In psychiatric manifestations of AE, EEG abnormalities have been identified less frequently in 33%–61% of cases, and MRI alterations have been identified in 51%–57% of cases (6, 9, 10, 32). However, there has been a limited application of advanced EEG approaches—including automated analysis pipelines in which independent component analysis (ICA) is used to detect intermittent rhythmic delta and theta activity (IRDA/IRTA), as well as quantitative structural MRI analyses that use morphometric approaches—to suspected AP spectrum syndrome patient groups. A systematic literature search using the terms “(autoimmune psychosis OR autoimmune psychiatric syndrome) AND (morphometry OR morphometric OR structural MRI OR CAT12 OR FreeSurfer OR IRDA OR IRTA OR EEG slowing OR independent component analysis)” (conducted on August 4, 2025) yielded 40 hits. Among these papers, there were no comparable multimodal approaches to autoimmune-mediated psychiatric patient cohorts.

The rationale of this exploratory study was to investigate EEG and morphometric MRI data in patients with suspected AP spectrum

syndromes compared to healthy controls (HC). Moreover, the study sought to analyze the correlation of morphometric MRI findings with EEG slowing, CSF changes, and psychometric/neuropsychological data. Previous studies in the field of immunopsychiatry have mainly described conventional MRI findings from case series (9, 10). The present research comprises the first multimodal brain imaging study to employ automated EEG and advanced morphometric MRI analyses. From the clinical and research perspectives, such multimodal approaches are essential for an in-depth investigation of the influence of autoantibodies on brain function.

Participants and methods

This project received approval by the Ethics Committee of the University Medical Center Freiburg (application no. EK-Freiburg: 209/18). Written informed consent was obtained from all patients and controls. This subproject was part of a larger transdiagnostic study in which multimodal brain imaging with a focus on IRDA/IRTA effects was conducted.

Patient assessment

The suspected AP spectrum syndrome cohort was recruited from current or former patients of the Department of Psychiatry and Psychotherapy of the Medical Center at the University of

Freiburg, Germany. All suitable patients whose initial diagnosis occurred within the last 10 years were offered participation in this study with further advanced MRI/EEG measurements and a broad psychometric/neuropsychological test battery. Adult patients (aged ≥ 18 years) with suspected AP spectrum syndromes—characterized by predominant classical schizophreniform syndromes and predominant affective spectrum syndromes with suspected autoimmune pathophysiology—were included. All patients were positive for well-characterized neuronal antibodies (e.g., against the NMDA-R) or had novel CNS antibodies in a tissue-based assay on unfixed mouse brain slices (e.g., against vessels or granule cells; Figure 1). In addition, patients with well-characterized systemic antibodies (i.e., antinuclear antibodies [ANAs] measured on human embryonic kidney cells or thyroid antibodies) and clear signs of brain involvement in further diagnostic testing (i.e., who were diagnosed as neuropsychiatric lupus or Hashimoto encephalopathy; 1, 33) were included. The term suspected AP spectrum syndromes was clinically used broadly (in the current international consensus recommendations no definition of psychosis is given) (2). Antibody-associated processes do not necessarily follow the diagnostic criteria of primary psychiatric disorders. Other authors have therefore proposed the more global term APS (8, 11). This APS concept was followed here, focusing in particular on a putative common autoimmune pathomechanism – which was suspected in all patients – rather than the identical clinical phenotype. This means that not only patients with acute-onset first episode paranoid hallucinatory

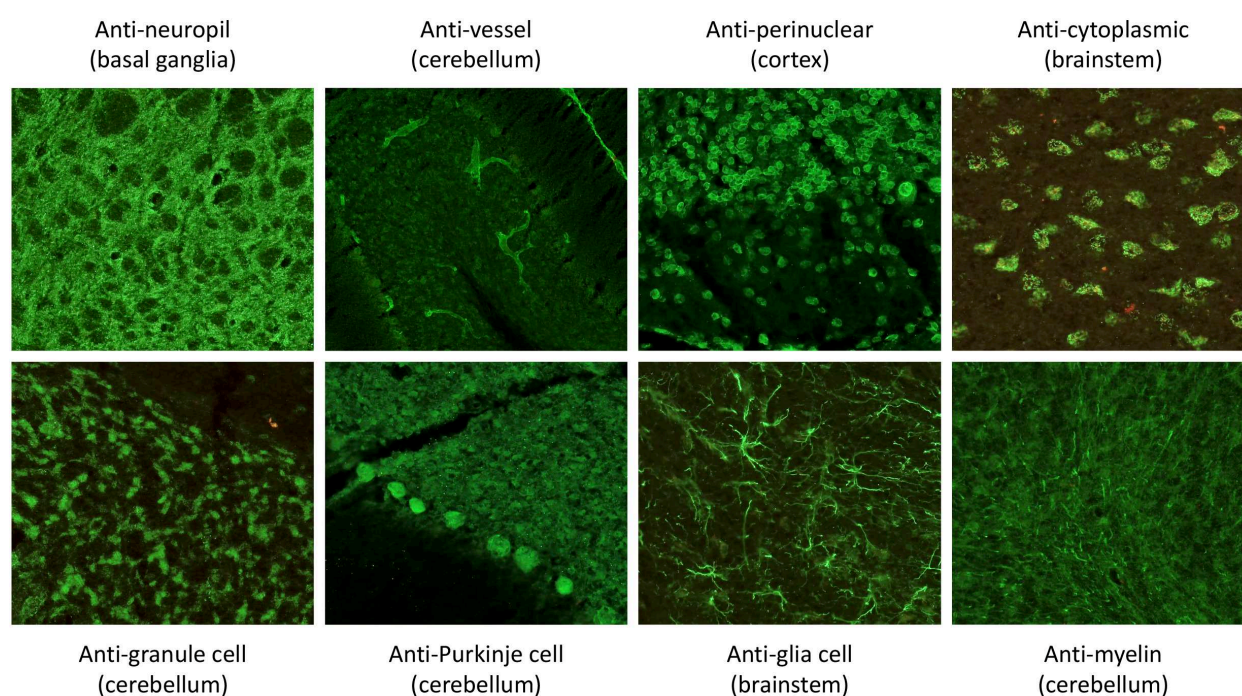


FIGURE 1

Exemplary antibody patterns using a tissue-based assay with unfixed mouse brain tissue (34), which led to inclusion in the study. This included antibody staining against the following structures: Neuropil, vessels, perinuclear and cytoplasmic structures, granule cells, Purkinje cells, glial cells, and myelin fibers. The brain region from which the antibody finding was obtained is shown in brackets. However, the staining patterns could of course also have been positive in other regions.

psychosis, but also patients with chronic symptoms and with predominant affective/neurocognitive/obsessive-compulsive syndromes were studied. If neurocognitive symptoms were present in addition to psychosis or as predominant syndrome, “predominant schizophreniform psychoses subgroup” was coded. Obsessive-compulsive syndromes in combination with affective syndromes were classified within the “predominant affective spectrum syndrome subgroup” (as was one severe obsessive-compulsive syndrome with pre-diagnosed comorbid depressive syndrome earlier in the course). Acutely ill, chronically ill and (partially) remitted patients were studied. Immunotherapy could also have been administered before the research MRI/EEG. Three subgroups according to the disease state were divided for further secondary analyses (Acute stage: current severe symptoms; Chronic stage: symptom duration exceeding 2 years; [Partially] improved: clinically documented symptom reduction following treatment). The use of psychopharmacological medication (including anticonvulsants) was recorded but did not lead to exclusion from the patient group.

As part of the diagnostic workup, patients underwent CSF analysis, conventional MRI evaluated by neuroradiology specialists, and serum and CSF antibody testing. Routine CSF parameters included WBC count, protein, albumin quotient, IgG index, and OCBs. Well-characterized neuronal antibodies against intracellular antigens were tested in serum by immunoblot (Ravo[®], Freiburg, Germany) and against cell surface antigens in serum and CSF using a fixed, cell-based assay (Euroimmun[®], Lübeck, Germany). In addition, most patients were tested for novel CNS antibodies using a tissue-based assay with unfixed mouse brain tissue (34). Many patients also underwent [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET; 22) as part of the clinical diagnostic work-up.

Pregnancy and lactation were defined as exclusion criteria. Subjects were also excluded if they lacked the legal capacity and ability to understand the nature, significance, and scope of the study or if they met relevant exclusion criteria for MRI examinations (pacemakers, intrauterine contraceptive devices, claustrophobia, etc.).

Healthy control group assessment

The recruitment of the HC group was conducted via public announcements. Individuals who met the criteria for the HC group and were aged ≥ 18 years were included in the study. Individuals with a lifetime diagnosis of a DSM-IV axis I or II disorder (as determined by questionnaire and through objective assessment using the SCID-I screening and SCID-II testing for borderline personality disorder), as well as those currently or previously taking psychopharmacological medications or other drugs within the past six months, were excluded from participation. The use of cannabis on an episodic basis did not result in exclusion from the study. Pregnancy and lactation were defined as exclusion criteria, as well as any known relevant physical comorbidities that might influence the outcome measures. Therefore, a history of brain injury, seizures/epilepsy, (meningo)encephalitis, hydrocephalus, or

space-occupying processes, was deemed grounds for exclusion. Furthermore, individuals with autoimmune diseases undergoing immunotherapy (e.g., steroids, azathioprine) or systemic autoimmune diseases with the potential for brain involvement (e.g., lupus erythematosus) were excluded from the study. Additionally, individuals were deemed ineligible if they lacked the capacity to comprehend the objectives, scope, and procedures of the study or if they met the criteria for exclusion regarding MRI (e.g., pacemaker, intrauterine contraceptive device or claustrophobia).

Sociodemographic, psychometric and neuropsychological testing

The socio-demographic data were collected using a structured questionnaire. The psychometric testing included a screening using the Structured Clinical Interview for DSM-IV (SCID-I/SCID-II) (35), Eppendorfer Schizophrenia Inventory (ESI) (36), Beck Depression Inventory II (BDI-II) (37, 38), State-Trait-Anxiety-Inventory (STAI-G) (39), Symptom-Checklist (SCL-90-R) (40), Wender Utah Rating Scale (WURS) (41), ADHD-Checklist for DSM-IV (ADHD-CL) (42), Asperger Questionnaire (AQ) (43), Empathy quotient (EQ) (44), and Positive and Negative Syndrome Scale (PANSS) (45). The neuropsychological test battery consisted of the Test for Attentional Performances (TAP) (46), Verbal Learning and Memory Test (VLMT) (47), and the Culture Fair Intelligence Testing (CFT-20 R) (48). Missing questionnaires or neuropsychological test results did not result in exclusion from the study if the aforementioned inclusion criteria were met and a clear clinical diagnosis was established. Patients and controls were matched using an automatic approach on basis of age and sex on the group level. The matching process and the final study group are summarized in Figure 2.

MRI measurement and analyses

The MRI measurements were all performed using the same Magnetom Prisma 3 T system (Siemens Healthineers[®], Erlangen, Germany) at the Imaging Center of the Department of Radiology of the University Medical Center Freiburg, Germany. A 64-channel head and neck coil was used for signal reception. Morphometric analyses were based on a high-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence with the following parameters: Field of view=256×256×160 mm³, voxel size=1×1×1 mm³; repetition time=2000 ms, echo time=4.11 ms. The Computational Anatomy Toolbox - version 12 (CAT12) was used to measure global volumes and cortical thickness (<http://dbm.neuro.uni-jena.de/cat/>) and subcortical analyses were based on FreeSurfer (7.2) (49; <https://www.freesurfer.net/fswiki/FreeSurferWiki>). CAT12 was used to process and spatially normalize T1-weighted MR images to extract global volumes and cortical thickness estimates. FreeSurfer, which includes a routine called “recon-all” that implements all the necessary steps to pre-process T1-weighted MR images, was used to extract volumes of

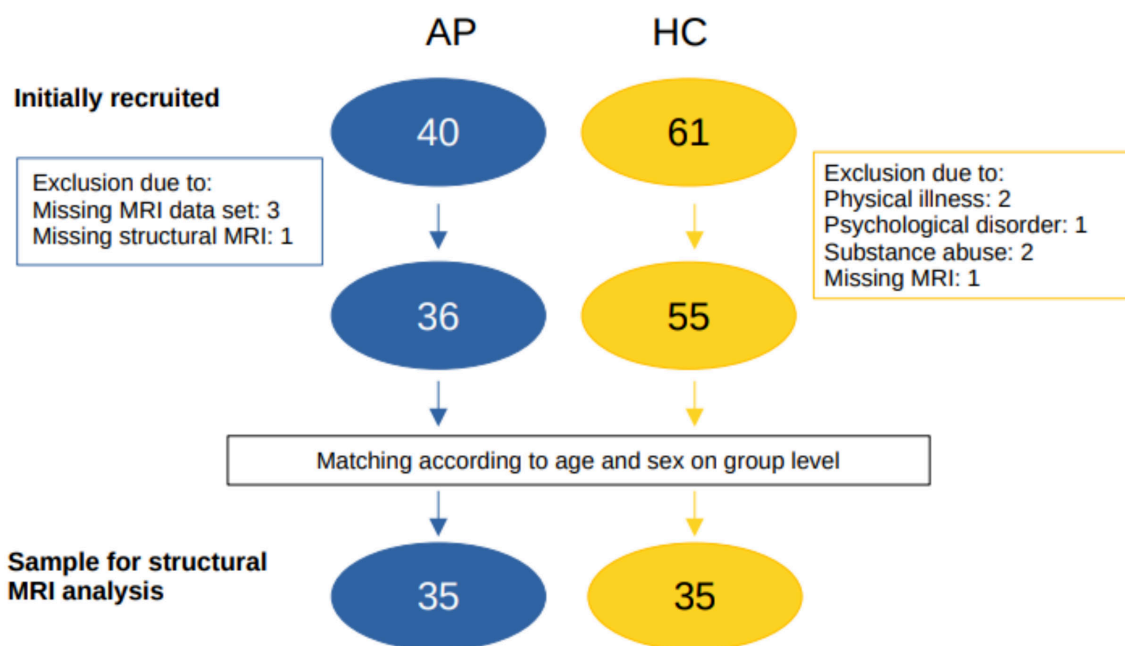


FIGURE 2

Recruitment flowchart for the group with available advanced MRI data (for the comparison of the electroencephalographic findings, 37 patients could be matched). AP, autoimmune psychosis; HC, healthy controls; MRI, magnetic resonance imaging.

subcortical structures (50). This combined approach using CAT12 and FreeSurfer is consistent with the conclusions of a recently published paper in which the two methods were compared (50). To further investigate the spatial pattern of AP-related changes in grey matter (GM) volume (51, 52), a voxel-based group comparisons of the CAT12-derived CSF tissue probability maps with age as nuisance covariate as implemented in the Statistical Parametric Mapping-Voxel-Based Morphometry 8-Toolbox and threshold-free cluster enhancement (53; <https://github.com/markallenthornton/MatlabTFCE>) was carried out. The family-wise error-method was employed to correct for multiple comparisons (i.e., across voxels).

EEG measurement and analysis

To record the EEG measurements, a Nihon Kohden Neurofax EEG-1200 system (Nihon Kohden Corp., Tokyo, Japan) with a 10–20 electrode montage (21 Ag-AgCl sintered bridge electrodes) was used. The analog filters were set between 0.1 and 30 Hz, and the data were digitized at a rate of 200 Hz. Electrode impedances were kept below 5kΩ. EEG recording lasted for 11 minutes and included eye-opening and -closing maneuvers and a three-minute hyperventilation (HV) episode. No photostimulation was performed. The IRDA/IRTA rates were determined after using ICA to separate eye movement artifacts as well as possibly multiple IRDA/IRTA components with different origins, using in-house software (https://github.com/berndf/avg_q, 54). To begin this process, artifacts were detected by identifying large amplitudes, large derivatives (“jumps”), and successive points with negligible variation (“blocking”). The five seconds before and after any artifact

or EEG start/stop event were marked for exclusion from the analysis. The remaining artifact-free EEG sections were then used for ICA training. Detection of IRDAs/IRTAs in the non-artifact ICA components were counted if they exceeded a lenient amplitude threshold of 1 μV and occurred in the artifact-free sections. Finally, the number of IRDA/IRTA events per minute of artifact-free EEG was computed (i.e., the sum of IRDA and IRTA events, not the ratio between them). Notably, this method extracted IRDA/IRTA activity regardless of the location of its generators. IRDA/IRTA rates were calculated separately for the EEG sections before and after HV. The rate before HV and the difference after-before HV (IRDA difference) are then analyzed statistically (54, 55).

Statistical analyses

Statistical analyses were conducted using R software 3.6.0 (R software v.3.6.0, R Foundation for Statistical Computing Platform, Vienna, Austria). Group comparisons for categorical variables (e.g., sex) were carried out with Fisher’s exact test. A t-test for independent samples was used for dimensional clinical variables (e.g., age). Based on prior studies of NMDA-R encephalitis (26), it was assumed before the study began that our patient cohort would exhibit consistent clinical EEG abnormalities. However, this did not turn out to be true. The Shapiro–Wilk test was used to test for normal distribution. Automatically analyzed EEG slowing, meaning IRDA/IRTA rates, was compared using a Wilcoxon rank sum test. All thickness and volume measures were adjusted for the effects of age (linear and quadratic terms), sex, and image quality rating (IQR) using a linear model and the predict function in R,

TABLE 1 Detailed presentation of the detected antibody and clinical findings in patients with suspected autoimmune psychosis spectrum syndromes.

Suspected AP spectrum syndromes (N=35)	
Clinical routine findings	
Well-characterized anti-CNS or systemic antibodies*	11 (31%)
In serum overall	
Anti-LGI1	1 (2.9%)
Anti-NMDA-R	1 (2.9%)
Anti-MOG	2 (5.7%)
Anti-Yo	1 (2.9%)
Anti-CASPR2	1 (2.9%)
Anti-VGCC	1 (2.9%)
Anti-TPO	2 (5.7%)
ANAs	1 (2.9%)
In CSF overall	
Anti-LGI1	1 (2.9%)
Anti-NMDA-R	2 (5.7%)
Anti-MOG	0 (0%)
Anti-Yo	0 (0%)
Anti-CASPR2	0 (0%)
Anti-VGCC	0 (0%)
Anti-TPO	0 (0%)
ANAs	1 (2.9%)
Novel anti-CNS antibodies	24 (69%)
Positive tissue-based assay in serum and/or CSF overall*	
In serum overall	
Anti-vessel pattern	2 (5.7%)
Anti-granule cell pattern	2 (5.7%)
Anti-myelin pattern	3 (8.6%)
Anti-Purkinje cell pattern	0 (0%)
Anti-cytoplasmic pattern	2 (5.7%)
Anti-glia cell pattern	0 (0%)
Anti-axon initial segment pattern	1 (2.9%)
Anti-neuropil pattern	1 (2.9%)
Anti-perinuclear pattern	2 (5.7%)
Anti-hippocampal pattern	0 (0%)
In CSF overall	
Anti-vessel pattern	5 (14%)
Anti-granule cell pattern	4 (11%)
Anti-myelin pattern	3 (8.6%)
Anti-Purkinje cell pattern	2 (5.7%)
Anti-cytoplasmic pattern	1 (2.9%)
Anti-glia cell pattern	1 (2.9%)
Anti-axon initial segment pattern	1 (2.9%)
Anti-neuropil pattern	1 (2.9%)
Anti-perinuclear pattern	3 (8.6%)
Anti-hippocampal pattern	2 (5.7%)
Syndrome overall	
Predominant schizophreniform syndromes**	18 (51%)
Predominant affective spectrum syndromes***	17 (49%)
Duration of illness	
Acute stage****	10 (29%)
Chronic stage (> 2 years)	11 (31%)
(Partially) improved by treatment	14 (40%)
Current psychiatric medication (< 6 month)	
Atypical antipsychotics	20 (57%)
Typical antipsychotics	5 (14%)
Antipsychotics	21 (60%)
Antidepressants	14 (40%)
Mood stabilizers	6 (17%)
Anticonvulsants	5 (14%)
Benzodiazepines	4 (11%)

(Continued)

TABLE 1 Continued

Suspected AP spectrum syndromes (N=35)	
Clinical routine findings	
Previous psychiatric medication (> 6 month)	
Atypical antipsychotics	16 (47%)
Typical antipsychotics	2 (5.9%)
Antidepressants	21 (62%)
Mood stabilizers	2 (5.9%)
Anticonvulsants	9 (26%)
Benzodiazepines	8 (24%)
CSF findings (N=35)	
White blood cell count (/μl)	2.20 ± 1.92
- Increased	4 (11%)
Protein concentration (mg/l) (N=34)	439 ± 214
- Increased	12 (34%)
Albumin quotient	6.57 ± 4.33
- Increased	11 (31%)
IgG-Index	0.54 ± 0.16
- Increased	2 (5.7%)
OCBs in serum	0 (0%)
OCBs in CSF	4 (12%)
CSF abnormalities	18 (51%)
Clinical EEG pathologies (N=35)	
Focal slowing	1 (4%)
Generalized slowing	12 (34%)
Intermittent slowing	11 (31%)
Continuous slowing	1 (3%)
Spike wave activity	0 (0%)
Overall EEG alterations	13 (37%)
Clinical routine brain imaging findings	
Clinical routine MRI changes (N=35)	
Non-specific white matter changes	26 (74%)
(Chronic) inflammatory lesions	3 (9%)
Global atrophy	6 (17%)
Focal atrophy	5 (14%)
Pineal cysts	6 (17%)
Others	6 (17%)
Overall MRI alterations	28 (80%)
FDG-PET alterations (N=23)	
Hypermetabolism	6 (26%)
Hypometabolism	8 (35%)
Overall FDG-PET alterations	12 (52%)

*Only the predominant antibodies were mentioned (in the event that several antibodies were present). **Three patients had additional severe neurocognitive syndromes, in one further patient the predominant neurocognitive syndrome was the leading clinical syndrome (but the patient was pre-diagnosed with psychosis) ***Seven patients had additional obsessive-compulsive syndromes and one patient had a leading severe obsessive-compulsive-syndrome (without current affective syndrome, but with pre-diagnosed additional depression) ****Five cases received immunotherapy. AP, Autoimmune psychosis; CSF, Cerebrospinal fluid; CNS, central nervous system; EEG, Electroencephalography; FDG-PET, Fluorodeoxyglucose positron emission tomography; IgG, Immunoglobulin G; MRI, Magnetic resonance imaging; OCB, oligoclonal bands.

standardizing the data to the mean age and mean IQR value of the sample. The “predict” function was used in two ways: first, without specifying new data, to obtain each subject’s fitted value from the model, which was then subtracted from the observed value; and second, with new data corresponding to target covariate levels (the sample’s mean age, IQR, predefined sex, and total intracranial volume [TIV]) to obtain the model’s predicted value at those reference levels. The adjusted value was computed as the observed value minus the fitted value plus the prediction at the reference

TABLE 2 Clinical and psychometric characteristics of the study cohort and comparison of patients with suspected autoimmune psychosis (AP) spectrum syndrome and healthy control (HC) group.

	Suspected AP spectrum syndromes (N=35) ¹	HC (N=35) ¹	p-value ²
Clinical data			
Age in years	41 ± 15 (N=35)	35 ± 11 (N=35)	0.058
Sex			
female (%)	18 (51%) (N=35)	20 (57%) (N=35)	0.800
male (%)	17 (49%) (N=35)	15 (43%) (N=35)	
Body information			
BMI (kg/m ²)	25.8 ± 4.2 (N=35)	22.6 ± 2.5 (N=35)	<0.001
Handedness			0.600
- both	2 (7%) (N=29)	1 (2.9%) (N=35)	
- left	2 (7%) (N=29)	4 (11%) (N=35)	
- right	25 (71%) (N=29)	30 (86%) (N=35)	
Mother tongue			
German	34 (97%) (N=35)	33 (94%) (N=35)	>0.900
Chinese	0 (0%) (N=35)	1 (3%) (N=35)	
Romanian	1 (3%) (N=35)	1 (3%) (N=35)	
Academic degree			
University degree	8 (23%) (N=35)	23 (66%) (N=35)	0.001
High degree	9 (26%) (N=35)	8 (23%) (N=35)	
Middle degree	11 (31%) (N=35)	4 (11%) (N=35)	
Low degree	2 (6%) (N=35)	0 (0%) (N=35)	
Other qualification	5 (14%) (N=35)	0 (0%) (N=35)	
Current employment status			
Full-time job	2 (6%) (N=35)	15 (43%) (N=35)	0.001
Part-time job	8 (23%) (N=35)	9 (26%) (N=35)	
Student	4 (11%) (N=35)	8 (23%) (N=35)	
Trainee	1 (3%) (N=35)	2 (6%) (N=35)	
Pensioner	13 (37%) (N=35)	0 (0%) (N=35)	
Unemployed	7 (20%) (N=35)	1 (3%) (N=35)	
Psychometric scores			
Questionnaire	p-value ²	Questionnaire	p-value ²
PANSS		ESI	
PANSS sum (33/35)	<0.001	ESI attention and speech impairment (30/34)	0.001
PANSS positive (34/35)	<0.001	ESI auditory uncertainty (31/34)	0.023
PANSS negative (33/35)	<0.001	ESI deviant perception (31/34)	0.035
PANSS general (34/35)	<0.001	ESI ideas of reference (30/33)	0.029
		ESI frankness (30/34)	>0.900
BDI-II (32/35)	<0.001	SCL-90-R (32/35)	
EQ (32/35)	0.4	Hostility	0.007
AQ (32/35)	<0.001	Anxiety	<0.001
WURS (29/35)	0.3	Depression	<0.001
ADHD-Checklist (28/34)	<0.001	Somatization	0.004
STAI-G Trait (32/35)	<0.001	Obsessive-compulsive	<0.001
		Interpersonal sensitivity	0.006
		Phobic anxiety	0.002
		Paranoid ideation	0.012
		Psychoticism	0.002

¹Mean ± SD; n (%). ²Welch Two Sample t-test or Fisher's exact test or Wilcoxon rank sum test. ADHD, Attention deficit hyperactivity disorder; AP, Autoimmune psychosis; AQ, Autism Quotient; BDI-II, Beck Depression Inventory II; BMI, Body Mass Index; ESI, Eppendorfer Schizophrenia Inventory; EQ, Emotional quotient; HC, Healthy controls; PANNS, Positive and Negative Syndrome Scale; SCL-90R, Symptom Checklist-90-R; STAI-G, State-Trait Anxiety Inventory; WURS, Wender Utah Rating Scale. Significant group differences are marked in bold.

covariate levels. A robust two-sample trimmed t-test for unequal population variances was used for group comparisons of morphometric brain imaging data (56), as the data were predominantly not normally distributed. In addition, effect sizes (Cohen's D) were calculated using R (57–59). Correlation analyses

were performed using the *pbcor* function from the *WRS2* package in R to compute the percentage bend correlation coefficient. For the correlation with the neuropsychological findings, age adjusted neuropsychological raw data were used. Therefore, all raw TAP subtest scores were screened for potential age and sex influences

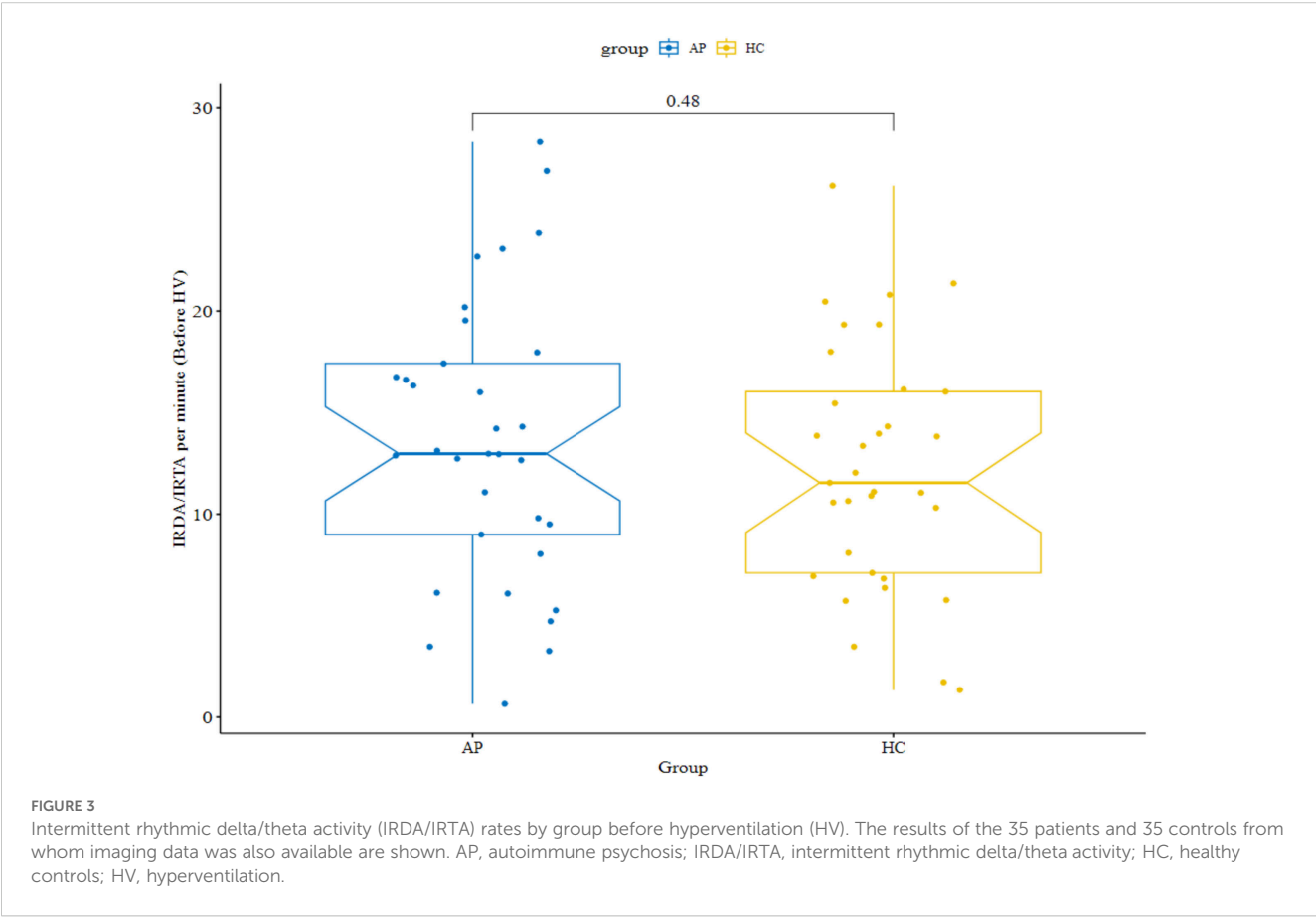
TABLE 3 Neuropsychological characteristics of the study cohort and comparison of patients with suspected autoimmune psychosis (AP) spectrum syndrome and healthy control (HC) group.

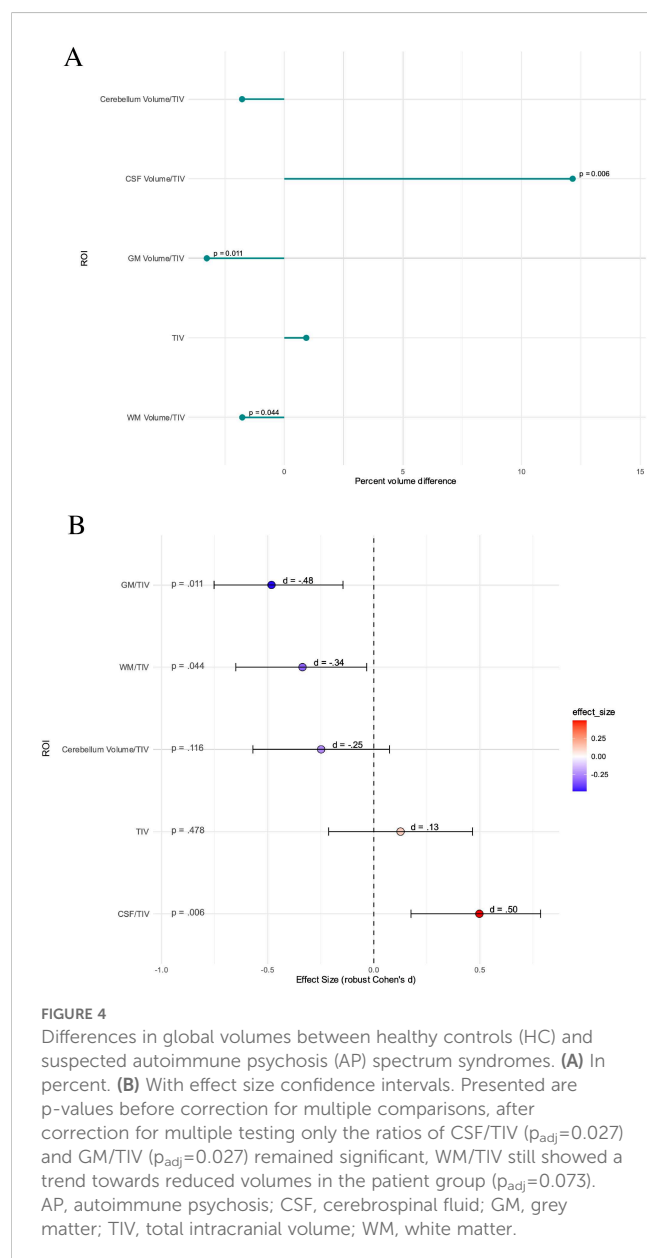
Test	p-value ¹	Test	p-value ¹
Neuropsychological findings			
TAP			
Alertness no warning tone (28/34)	0.034	VLMT VLMT learning (35/35) VLMT false positive (34/35) VLMT preservations (34/35) VLMT recognition (33/35) VLMT Consolidation (33/35)	<0.001 0.095 0.274 <0.001 <0.001
Alertness warning tone (28/34)	0.081		
Phasic alertness (28/34)	0.088		
Working memory mistakes (28/34)	0.007		
Working memory missings (28/34)	0.001		
Mental flexibility (27/34)	0.001		
Divided attention mistakes (27/34)	0.036		
Divided attention missings (27/34)	0.003		
CFTR-20 IQ (24/31)	<0.001		

¹Welch Two Sample t-test or Fisher's exact test or Wilcoxon rank sum test. AP, Autoimmune psychosis; CFTR-20, Culture Fair Intelligence Testing; HC, Healthy controls; TAP, Test of Attentional Performance; VLMT, Verbaler Lern- und Merkfähigkeitstest. Significant group differences are marked in bold.

with the Boruta feature-selection wrapper for the random forest algorithm; age emerged as an important predictor, while sex did not. Consequently, each raw score was regressed on age (lm[raw ~ age]), and an age-adjusted value for each participant was calculated as the residual plus the model prediction at the sample's mean age, similar to the “predict” approach mentioned above. These age-

corrected scores replaced the original t-scores and were used in subsequent analyses. The corrections for multiple testing were performed for all tests according to the Benjamini–Hochberg approach (60). A significance level of $p < 0.05$ was applied. All corrected p-values are described as adjusted (“ p_{adj} ”) to distinguish them from the uncorrected p-values (“p”) that are also reported.





Results

Patient and control group

A total of 35 patients with MRI data (mean age: 41 ± 15 years; 51% female) were included, alongside 35 age- and sex-matched HCs. No significant differences were identified in age ($p=0.06$) or sex ($p=0.80$) compared to the HC group. The patient sample was almost evenly split between predominant classical schizophreniform syndromes in 51% and predominant affective spectrum syndromes in 49%. Overall, eleven patients (31%) had well-characterized antibodies and 24 patients (69%) novel anti-CNS antibodies in serum and/or CSF. Antibody testing in CSF was positive in 77% (in 27 from 35 cases) of the entire patient group. Clinical routine MRI alterations were detected in 80% (without non-specific white matter

changes or other norm variants in only 29%), CSF routine pathologies in 51%, FDG-PET (only available in $n=23$) hyper/hypometabolism in 52%, and clinical EEG alterations in 37%. The detailed clinical syndromes, diagnostic findings, including different autoantibodies and medications, are summarized in [Table 1](#). Only 29% of the included patients were in an acute stage, of which five patients had already received immunotherapy. In total, twenty-two patients (63%) received immunotherapies before MRI scanning (no acute immunotherapies were administered during the time of MRI). While the HC group received no medication, suspected AP spectrum syndrome patients were most likely to receive additional antipsychotics (60%) and antidepressants (40%). On the psychometric PANSS, ESI, BDI-II, AQ, ADHD-CL, SCL-90-R, and STAI-G, the patient group scored significantly higher. For the neuropsychological testing including TAP, the VLMT, and the CFT20-R various significant differences with generally more pathological scores in the patient group in contrast to HCs have been detected ([Tables 2, 3](#)).

Electroencephalography findings

Among the 35 patients with available MRI data and their matched controls, IRDA/IRTA rates were not significantly different, i.e., events per minute before HV (14.0 ± 7.0 in AP vs. 12.0 ± 6.0 in HC; $p=0.483$), and the IRDA/IRTA difference (1.8 ± 4.8 in AP vs. 3.1 ± 4.3 in HC; $p=0.194$) ([Figure 3](#)). In the slightly larger EEG subset of 37 patient-control pairs (including those without MRI data), the negative findings with IRDA/IRTA rates per minute before HV (13.6 ± 6.0 in AP vs. 11.9 ± 5.9 in HC; $p=0.220$) and IRDA/IRTA difference (1.9 ± 4.7 in AP vs. 3.4 ± 4.2 in HC; $p=0.102$) remained consistent.

Global magnetic resonance imaging volumes

The analysis of global brain volumes showed increased ratios of CSF/total intracranial volume (TIV) ($p=0.006$) and reduced ratios of GM/TIV and WM/TIV in the patient group ($p=0.011$ and $p=0.044$, respectively). TIV did not differ significantly between groups, and cerebellar volume also showed no significant group differences ([Figure 4](#)). After correction for multiple testing, only the ratios of CSF/TIV ($p_{adj}=0.027$) and GM/TIV ($p_{adj}=0.027$) remained significant, WM/TIV still showed a trend towards reduced volumes in the patient group ($p_{adj}=0.073$).

Cortical thickness

The analysis of cortical thickness identified widespread reductions with small effect sizes across almost all analyzed regions in the suspected AP spectrum group. Significant reductions were observed in the left parahippocampal gyrus

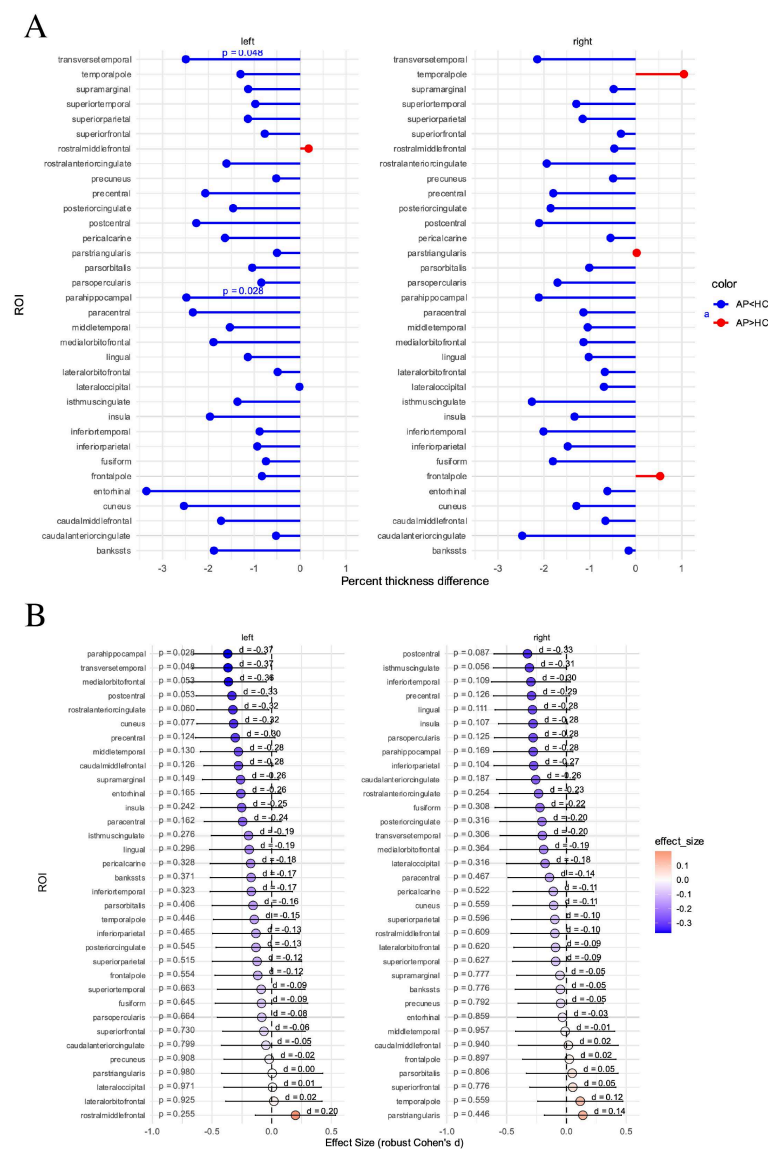


FIGURE 5

Differences in cortical thickness between healthy controls (HC) and suspected autoimmune psychosis (AP) spectrum syndromes. **(A)** In percent. **(B)** Effect size with confidence intervals. Presented are p-values before correction for multiple comparisons, after correction for multiple testing no significant differences remained (left parahippocampal gyrus: $p_{adj}=0.520$; left transversotemporal gyrus: $p_{adj}=0.520$). AP, autoimmune psychosis; HC, healthy controls; ROI, region of interest.

($p=0.028$) and the left transversotemporal gyrus ($p=0.048$) (Figure 5). However, these effects did not withstand the correction for multiple testing (left parahippocampal gyrus: $p_{adj}=0.520$; left transversotemporal gyrus: $p_{adj}=0.520$).

Subcortical volumes

The analysis of subcortical volumes revealed no significant differences, except for the left lateral ventricle, which was significantly enlarged in the patient group ($p=0.028$); however, the finding was not significant after correction for multiple testing ($p_{adj}=0.461$) (Figures 6, 7).

Subgroup analyses according to disease state

The different findings regarding global brain volumes, cortical thickness, and subcortical volumes (including those that were significant before correction for multiple testing) between the patient and the HC group were more precisely analyzed in a subgroup analysis of the suspected AP group with regard to disease state. Specifically, patients in the acute stage ($N=10$) were compared with those in the chronic stage ($N=11$) and those in the non-acute stage (chronic plus [partially] improved, $N=25$). No significant differences were found for CSF/TIV ($p=0.642$, $p=0.522$), GM/TIV ($p=0.637$, $p=0.589$), WM/TIV ($p=0.646$, $p=0.518$) ratios, cortical

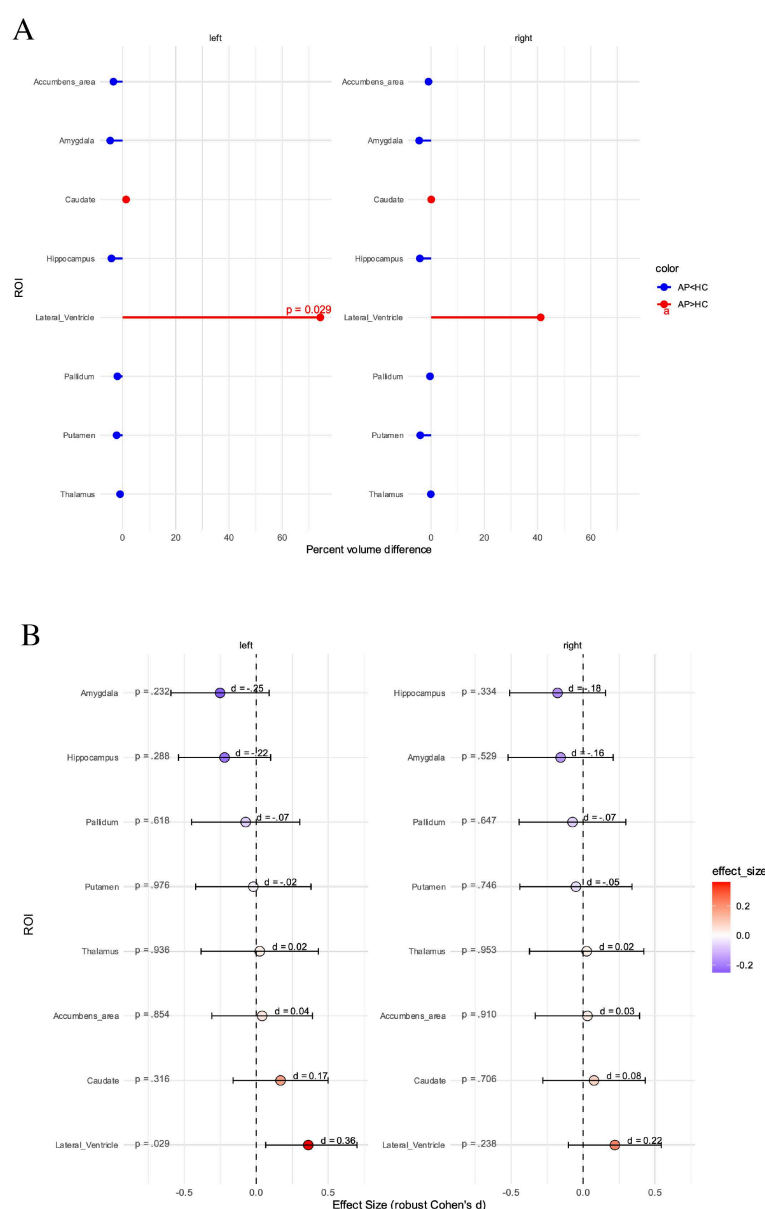


FIGURE 6

Differences in subcortical volume between healthy controls (HC) and suspected autoimmune psychosis (AP) spectrum syndromes. (A) In percent. (B) Effect size with confidence intervals. Presented are p-values before correction for multiple comparisons, after correction for multiple testing the differences for the left lateral ventricle no longer remained significant ($p_{adj}=0.461$). AP, autoimmune psychosis; HC, healthy controls; ROI, region of interest.

thickness of the left parahippocampal ($p=0.890$, $p=0.767$) and left transversotemporal ($p=0.578$, $p=0.454$) gyri, or the volume of the left lateral ventricle in either the acute vs. chronic or acute vs. non-acute comparisons ($p=0.253$, $p=0.094$).

Correlation analyses within the patient group

Electroencephalography

No significant correlations were identified between EEG slowing parameters and global MRI volumes. However, a higher

IRDA/IRTA rate per minute before HV in the EEG was associated with cortical thinning of the left caudal anterior cingulate cortex ($p<0.05$). The correlation of IRDA/IRTA rates with subcortical volumes revealed no significant findings (Figure 8).

Cerebrospinal fluid

Global MRI volumes and cortical thickness showed no significant associations with CSF findings. However, WBC count in CSF was positively correlated with larger volumes in the left and right hippocampus ($p<0.05$; Figure 9). An additional comparison of the WBC counts between the acutely ill and the non-acutely ($p=0.769$) or chronically ill ($p=0.705$) showed no significant

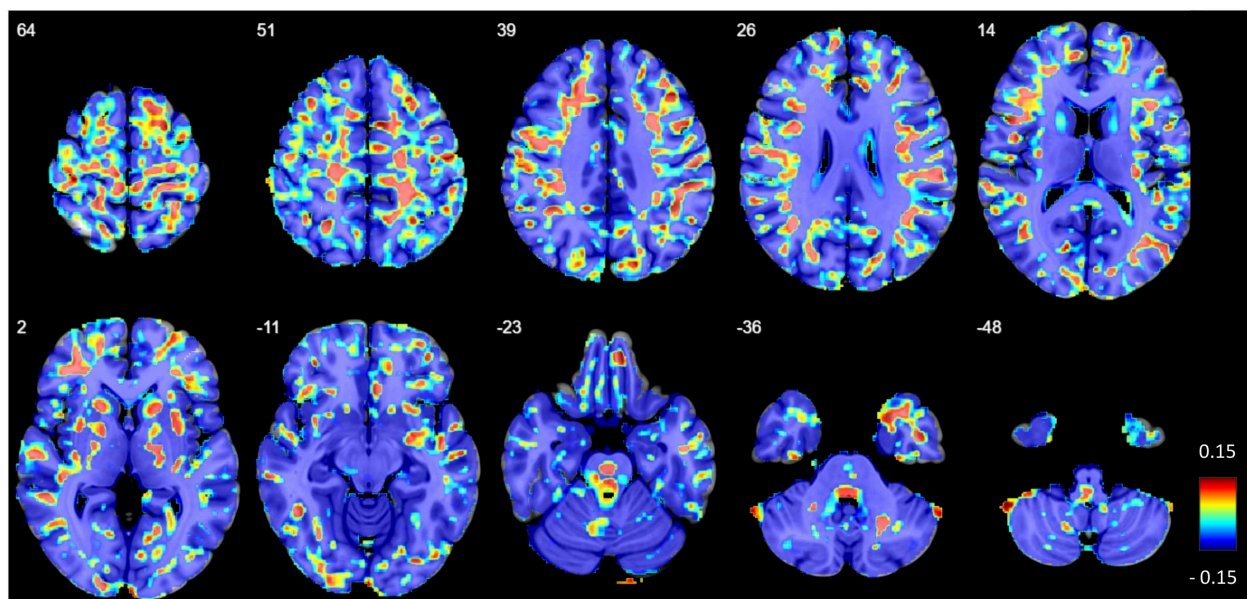


FIGURE 7

The standardized regression coefficients of the factor cerebrospinal fluid (CSF) were extracted from two-tailed linear regression models obtained from voxel-wise comparisons between suspected autoimmune psychosis (AP) spectrum syndromes and healthy controls (HC) and superimposed on a T1w magnetic resonance imaging (MRI) template. Color coding indicates coefficient values as a measure of the effect size of the AP factor (hot colors: positive effects vs. cold colors: negative effects).

group difference in the WBC counts. No significant correlation was identified between the advanced MRI parameters and the CSF markers for blood-brain barrier function (albumin quotient and protein concentration).

Psychometric findings

Correlations with the ESI and the PANSS were analyzed. No significant correlations were identified between both scores and global volumes, cortical thickness, or subcortical volumes (Figure 10).

Neuropsychological findings

Working memory mistakes in the TAP were negatively correlated with global GM volume ($p < 0.01$) and positively with global CSF volume ($p < 0.01$). Divided attention mistakes were negatively correlated with the cortical thickness of the right pars opercularis ($p < 0.05$) and the right transversotemporal cortex ($p < 0.05$). VLMT learning scores were positively correlated with the subcortical volume of the left ($p < 0.05$) and right putamen ($p < 0.01$) and the right hippocampus ($p < 0.05$) and negatively correlated with the volume of the right lateral ventricle ($p < 0.05$). The VLMT recognition score was negatively correlated with the volume of the right putamen ($p < 0.05$) and the VLMT consolidation score was negatively correlated with the volume of the left ($p < 0.05$) and right ($p < 0.01$) putamen (Figure 11).

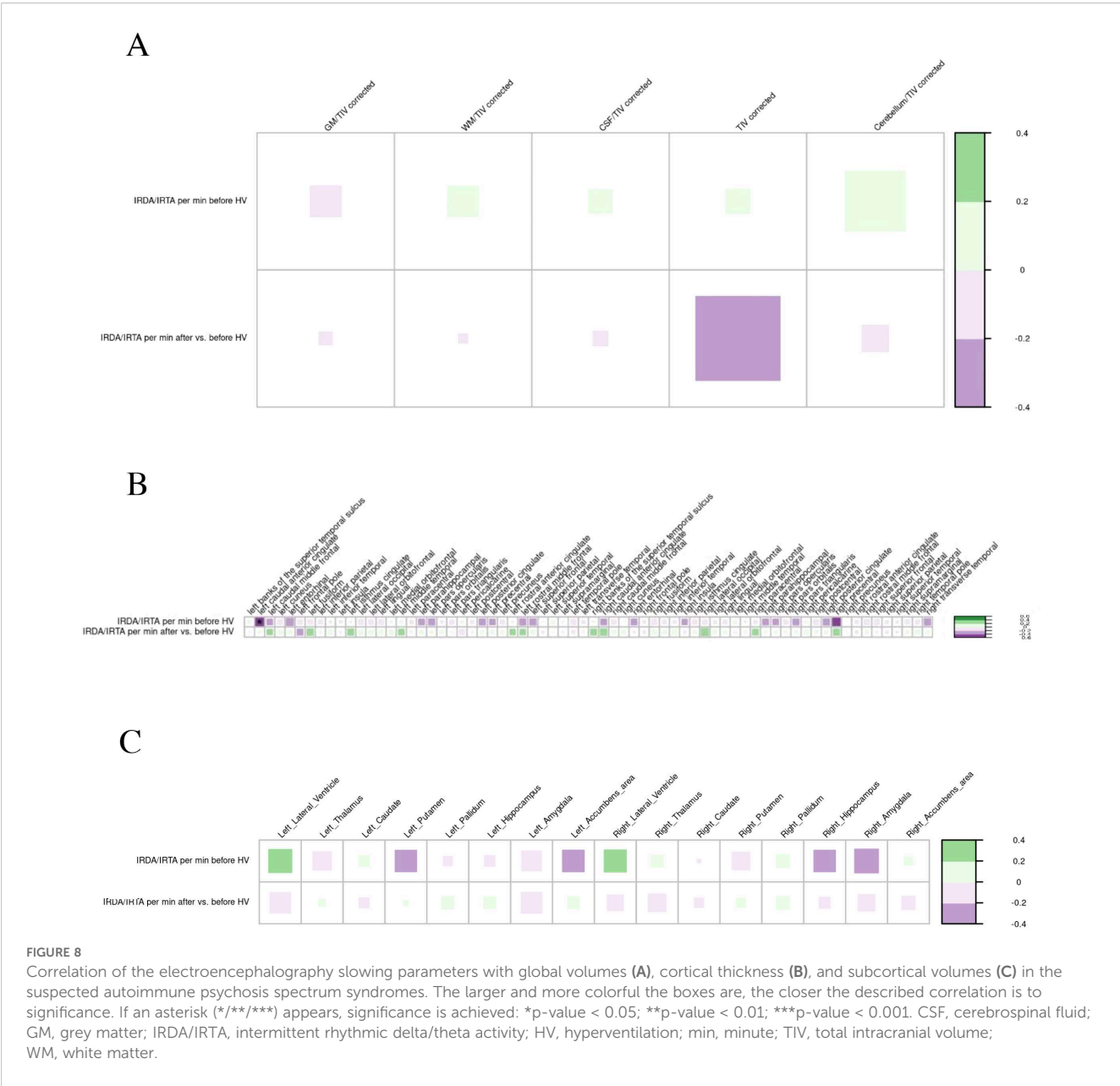
Discussion

The main findings of this study indicate no relevant EEG changes but global structural GM volume reductions in patients

with suspected AP spectrum syndromes. In the patient group, high IRDA/IRTA rates correlated with reduced volumes in the left caudal anterior cingulate gyrus. In addition, correlations between increases in hippocampal volume and inflammatory CSF markers were detected. Finally, the volumes of different brain areas, including the GM and right hippocampus, correlated with cognitive function but not with disease-specific scores.

EEG was initially interpreted as a sensitive diagnostic tool for the detection of AP (7) as up to 90% of patients with anti-NMDA-R encephalitis showed EEG pathologies (27, 28). Accordingly, pathologies in EEG such as IRDA and IRTA were included in the diagnostic criteria for AP (2). We therefore hypothesized to detect mostly conspicuous EEG findings, but contrary to our hypothesis, this was not the case. Indeed, the results of this work suggest that at least IRDA/IRTA rates do not reliably distinguish between suspected AP spectrum syndrome patients and HCs. The reason for this could be that milder, oligosymptomatic psychiatric forms of AE were investigated in this study. Pathological EEG findings may be more frequently detectable in neurological manifestations of AE (1). The correlation analyses showed that higher IRDA/IRTA rates in the suspected AP spectrum syndrome group were associated with reduced volumes of the left caudal anterior cingulate gyrus. Anterior cingulate epilepsies were described earlier (61), so this correlation might be compatible with the electrophysiological network instabilities generated in this brain region (62, 63).

In the global brain volume analyses, a reduction of GM volume, an increase of CSF volume, and a trend towards reduced WM volume were identified in patients with suspected AP spectrum syndromes. The detected findings would be consistent with a global loss of volume in the sense of a reduction of brain



tissue (GM and with a trend for WM) with secondary enlarged CSF spaces. MRI alterations extending beyond the limbic system have also been described for AE with well-characterized neuronal autoantibodies (31). The volume loss could be associated with the long course of the disease (31) and the late detection in many of the cases described here; however, this assumption could not be confirmed in the performed secondary analyses. Since even the acute cases did not have to have a subacute onset (<3 months), as suggested in the international consensus criteria for AP (2), these findings may nevertheless not be representative of acute AP cases (only 29% of the patients in this cohort were in an acute state).

Focal volume comparisons identified a trend for a reduced cortical thickness in the left parahippocampal gyrus and the left transversotemporal gyrus, as well as an increase of the left lateral ventricle volume. The temporal cortical regions are frequent targets

of CNS autoantibodies. This is indicated by the binding patterns of well-characterized neuronal autoantibodies on rat brain slices (30). However, these findings did not remain significant after correction for multiple comparisons. Increased hippocampal volumes, in contrast, were correlated with increased WBC counts in CSF. This finding could be the result of a slight autoimmune inflammatory limbic encephalitis component. Limbic encephalitis usually leads to edematous swelling of the medial temporal lobes in the initial stage (1, 64). Some of the patients in this group had antibodies (e.g., against LGI1) that can be associated with limbic encephalitis (1, 4, 5, 64). The novel antibody patterns against granule cells are also usually detected in the limbic system (as well as in the cerebellum and olfactory bulb) (65). As the disease progresses, the edema usually regresses and can even turn into atrophic changes if left untreated (55, 66, 67). Although limbic

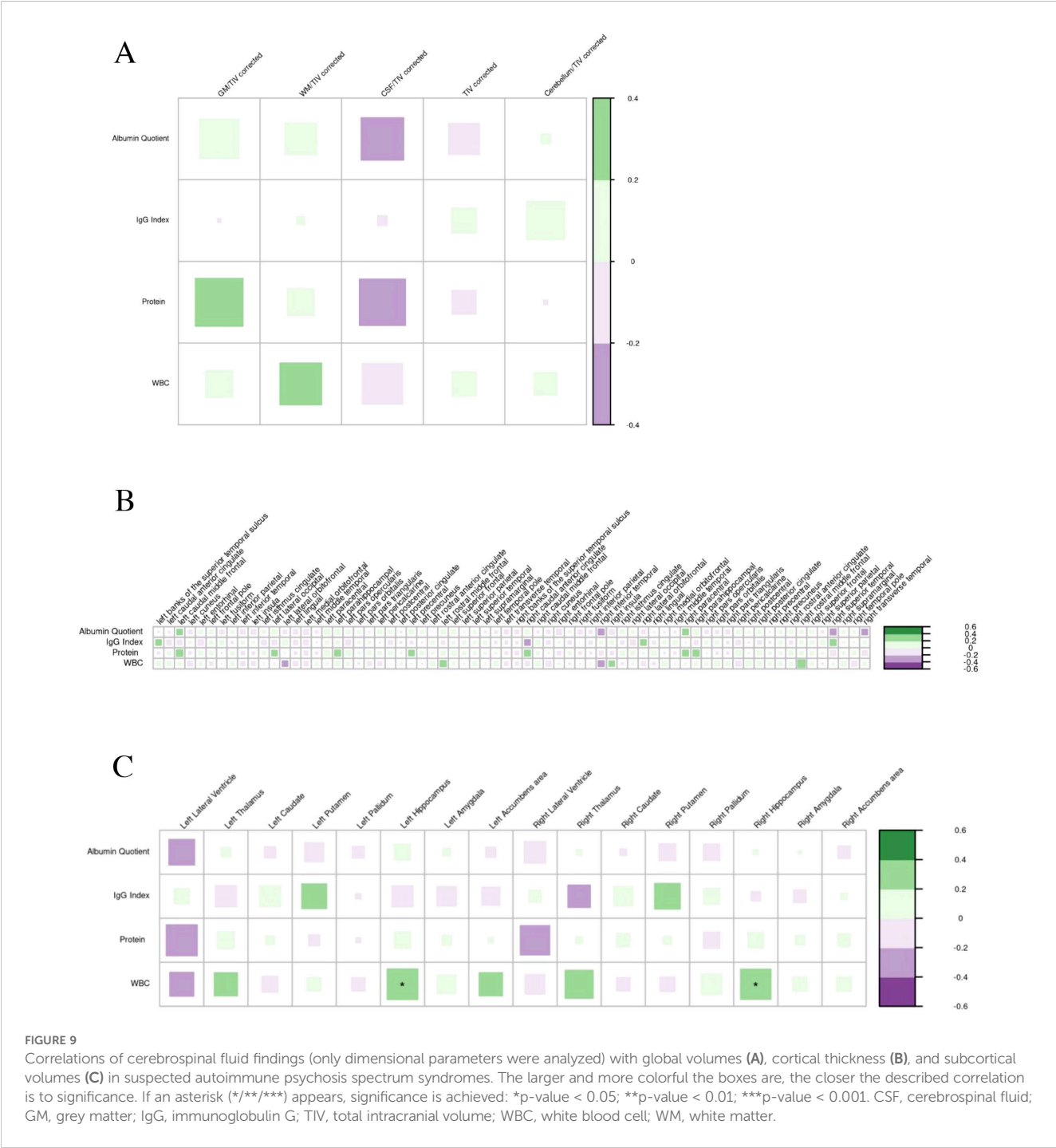
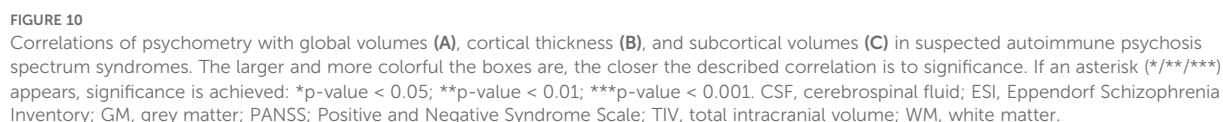


FIGURE 9
Correlations of cerebrospinal fluid findings (only dimensional parameters were analyzed) with global volumes **(A)**, cortical thickness **(B)**, and subcortical volumes **(C)** in suspected autoimmune psychosis spectrum syndromes. The larger and more colorful the boxes are, the closer the described correlation is to significance. If an asterisk (**/**/***) appears, significance is achieved: ***p-value < 0.05; ****p-value < 0.01; *****p-value < 0.001. CSF, cerebrospinal fluid; GM, grey matter; IgG, immunoglobulin G; TIV, total intracranial volume; WBC, white blood cell; WM, white matter.

encephalitis can lead to temporal atrophy at later stages, no such atrophy was detected in this particular patient group. In addition, there were no significant differences in the WBC counts between the acute and subacute/chronic cases. Thus, the correlation appears to be associated with specific antibodies rather than the stage of the disease.

From a clinical perspective, these findings suggest predominantly global volume loss in the suspected AP spectrum syndrome group. Accordingly, advanced MRI analyses could support the detection of global imaging patterns in autoimmune brain processes. In addition, morphometric analyses can be used to

detect hippocampal swelling and monitor the long-term course of a disease (68). However, the findings also reinforce the value of early detection and treatment, as volume loss has been associated with chronic progression in AE (17, 31). These imaging findings were correlated not with disease-specific scores (ESI or PANSS) but rather with cognitive function outcomes (on the TAP and VLMT). Thus, the alterations seem to be primarily associated not with clinical syndrome but instead with cognitive disability. In particular, a correlation was detected between low GM volume and more mistakes in working memory measurements. In addition, success in VLMT learning was positively correlated with right



The group suspected of AP spectrum syndromes was clinically heterogeneous, which must be acknowledged as a major limitation of the study. Conversely, this research uniquely identified uniform underlying autoimmunity in the patient group. Patients at different

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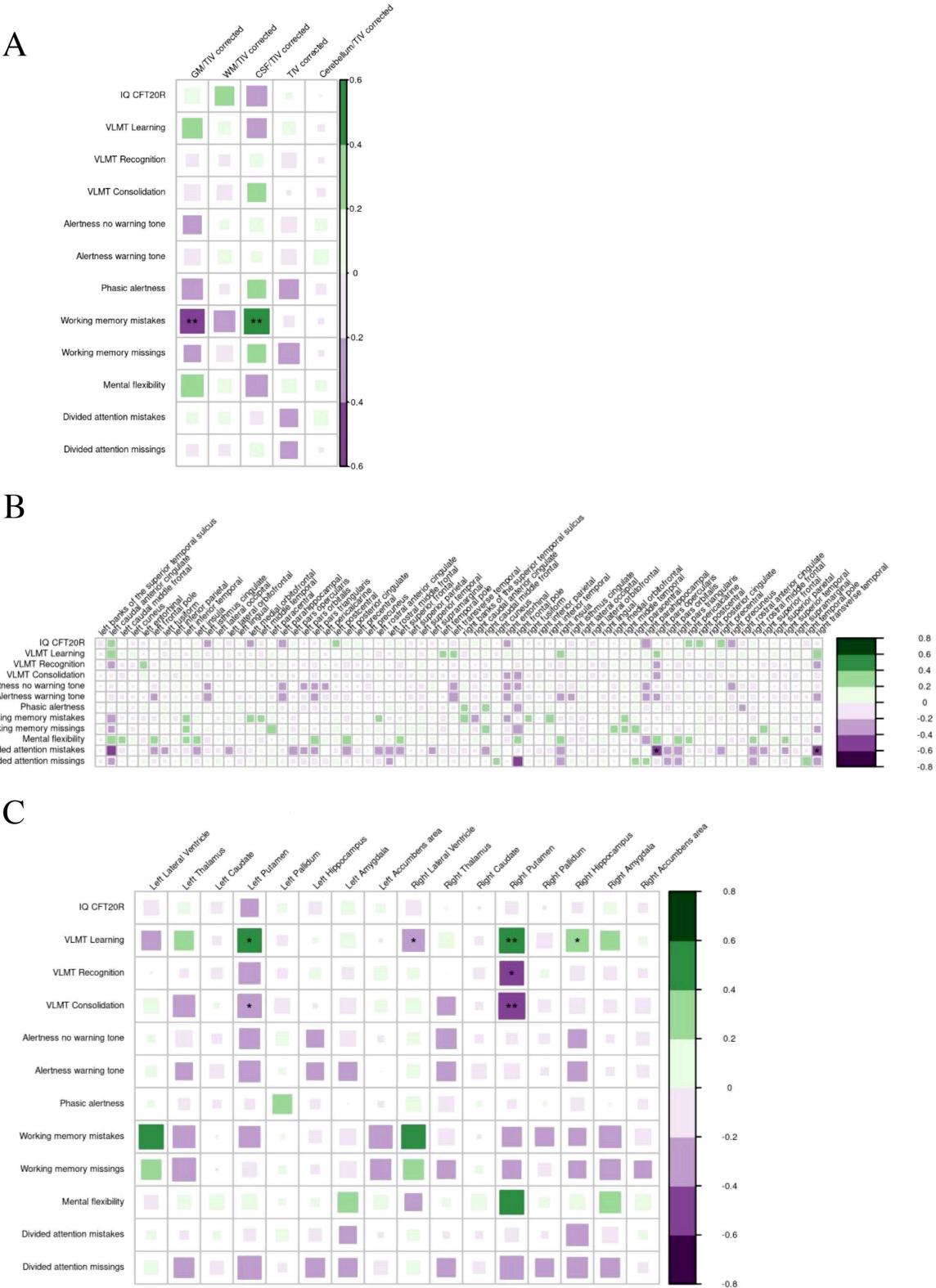


FIGURE 11
Correlation of neuropsychological findings with global volumes (A), cortical thickness (B), and subcortical volumes (C) in suspected autoimmune psychosis spectrum syndromes. The larger and more colorful the boxes are, the closer the described correlation is to significance. If an asterisk (*/**/****) appears, significance is achieved: *p-value < 0.05; **p-value < 0.01; ****p-value < 0.001. CSF, cerebrospinal fluid; GM, grey matter; IQ, intelligence quotient; TIV, total intracranial volume; WM, white matter; VLMT, Verbal Learning Memory Test; CFT20R, Culture Fair Intelligence Test 20.

clinical significance was still unclear, were also included. As a result, the study does not provide sufficient evidence for conclusions to be drawn about specific patient subgroups—for example, imaging findings regarding the psychiatric manifestations of NMDA-R encephalitis. However, these limitations were counterbalanced by a uniform suspected autoimmunity in all patients, which was postulated after a multimodal diagnostic work-up including EEG, CSF analysis, brain imaging, and autoantibody testing. For example, 77% of the patients had CNS autoantibodies in their CSF, which strongly suggests central autoimmunity. Patient groups with identical underlying autoimmunity are rare in psychiatry. For instance, in a systematic review of the literature on psychiatric manifestations of AE, only 145 cases were identified in the entire literature (10). Accordingly, it is currently highly difficult to monocentrically generate a uniform patient group with identical clinical syndromes, disease stages, and autoantibodies in the serum/CSF. However, our study is the first to provide overarching morphometric results for suspected AP spectrum syndrome patients.

As further limitations, the findings may be a consequence of long disease courses or influences of psychopharmacotherapy (albeit only in the patient group) in some cases and are therefore not generalizable to unmedicated first-episode psychosis patients. However, secondary analyses comparing patients at different disease stages—for example, acute versus nonacute or chronic—revealed no variation in the MRI group effects that were statistically significant. The inconspicuous EEG findings could also be attributed to the influence of menstrual cycle phases or to the fact that 63% of the patients had already received immunotherapies. A stratified analysis of the EEG and morphometric group comparisons based on antibody subtypes was not performed because the subgroups with identical CNS antibodies were too small. In addition, the HC group did not undergo CSF analysis or antibody testing. Thus, the results of this research—the first exploratory case-control study to apply morphometric MRI approaches to suspected AP spectrum syndromes—should be interpreted as preliminary findings that need to be replicated; they could also be used to generate further hypotheses. Future studies (ideally in multicenter settings) would benefit from larger sample sizes and more targeted approaches, such as examining patients with the same clinical syndrome and well-characterized CNS antibody at one clearly defined disease stage (e.g., the acute phase).

Conclusion

In summary, this study employed a multimodal approach—including automated EEG, advanced morphometric MRI analysis, and CSF, antibody, and psychometric/neuropsychological testing—to provide novel insights into morphometric alterations in patients with suspected AP spectrum syndromes and these alterations' association with cognitive, EEG, and CSF findings. Further immunopsychiatric research using advanced multimodal approaches holds strong potential to uncover specific diagnostic patterns.

Data availability statement

The raw data supporting the conclusions of this article can be made available by the authors on reasonable request.

Ethics statement

The studies involving humans were approved by Ethics Committee of the University Medical Centre Freiburg (no: 209/18). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

KZ: Resources, Visualization, Formal analysis, Data curation, Project administration, Methodology, Software, Writing – original draft, Investigation. LT: Conceptualization, Resources, Funding acquisition, Writing – review & editing, Supervision. BF: Supervision, Writing – review & editing, Conceptualization, Investigation, Software, Methodology, Funding acquisition, Visualization, Formal analysis. IM: Methodology, Writing – review & editing, Investigation, Data curation. AS: Project administration, Data curation, Writing – review & editing, Investigation. TL: Supervision, Methodology, Conceptualization, Writing – review & editing, Software, Resources. KR: Writing – review & editing, Data curation. KN: Data curation, Supervision, Methodology, Writing – review & editing. NV: Data curation, Supervision, Writing – review & editing. KD: Resources, Supervision, Writing – review & editing. HP: Formal analysis, Visualization, Supervision, Data curation, Methodology, Writing – review & editing. AR: Methodology, Software, Writing – review & editing, Visualization, Formal analysis. MR: Methodology, Writing – review & editing, Software. SM: Writing – review & editing, Formal analysis, Supervision, Methodology, Software, Resources, Visualization. DE: Conceptualization, Writing – review & editing, Supervision, Funding acquisition, Resources.

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Conflict of interest

KD: Member of the Neurotorium Editorial Board, The Lundbeck Foundation. She received speaker's honoraria by Janssen-Cilag GmbH. LT: Advisory boards, lectures, or travel grants within the last three years: Roche, Eli Lilly, Janssen-Cilag, Novartis, Shire, UCB, GSK, Servier, Janssen, and Cyberonics.

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