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Neuropsychological Long Term Decline Related to Silent Cerebral Lesions after Pulmonary Vein Isolation

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Abstract

Objectives: In this study, we aimed at investigating putative neuropsychological long term impairments of cognitive flexibility, verbal long term memory, and theory of mind in patients with atrial fibrillation depending on frontal silent cerebral lesions 6-9 years after pulmonary vein isolation with a pulmonary vein ablation catheter.

Background: The pulmonary vein ablation catheter (PVAC) shows an increased prevalence of developing silent cerebral lesions after pulmonary vein isolation in patients with atrial fibrillation.

Methods: 20 participants were medically and neuropsychologically examined and underwent MRI of the brain.

Results: Most lesions were located in the frontal lobes. Largeness of frontal lesions positively correlated with poorer verbal memory performance. Moreover, selective impairments of executive functions were associated with the extent of lesions. Symptom severity of atrial fibrillation correlated positively with impaired executive functions. Negative correlations were found between the risk of stroke and both executive functions and theory of mind.

Conclusion: These data demonstrate for the first time evidence for specific persisting long term impairments in verbal memory and selective executive functions related to silent cerebral lesions in the frontal lobes in patients with atrial fibrillation 6-9 years after ablation with a PVAC catheter. We propose that MRI and comprehensive neuropsychological assessment should be accomplished in clinical routines before, immediately after and at different follow up time points. Such longitudinal assessment may help to better understand the incidence and development of silent cerebral lesions and thus predict the risk of persisting cognitive disturbances in patients with atrial fibrillation treated with PVAC PVI and other pulmonary vein isolation methods.

Keywords: Pulmonary vein ablation • PVAC • Silent cerebral lesions • Persisting cognitive disturbance • Neuropsychological performance • Risk of stroke • MRI

Abbreviations

(PVAC) Pulmonary Vein Ablation Catheter; (SCL) Silent Cerebral Lesions; (PVI) Pulmonary Vein Isolation; (AF) Atrial Fibrillation; (FL) Frontal Lobe; (TOM) Theory of Mind; (IQ) Intelligence Quotient; (MRI) Magnetic Resonance Imaging; (FMRI) Functional Magnetic Resonance Imaging; (BDI) Beck's Depression Inventory; (STAI) State Trait Anxiety Inventory; (RMET) Reading the Mind in the Eyes Test; (TMT) Trail Making Test; (MMST) Mini Mental Status Test; (M) Mean; (SD) Standard Deviation; (CERAD) Consortium to Establish a Registry of Alzheimer's Disease; (FLAIR) Fluid Attenuated Inversion Recovery; (DWI) Diffusion Weighted Imaging; (ADC) Apparent Diffusion Coefficient; (ECG) Electrocardiogram

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia [1] and one of the most important health problems in the Western world [2]. Pulmonary vein isolation (PVI) is applied in non-responders of pharmacological treatment [3]. PVI increases the risk of stroke and the occurrence of silent cerebral lesions (SCL) [3-5]. However, little is known about the mechanisms leading to SCL during and/or after PVI. MRI studies show a varying prevalence of 7%-50% of SCL after PVI [6-8]. SCL are most frequently in the frontal and parietal lobes, as well as the cerebellum [7,9]. Only a few studies assessed development of SCL after PVI across several months. Deneke et al [10] showed that SCL after PVI may recover after 21 months. Rillig et al [11] compared the incidence and 21-months development of SCL after robotically assisted (RA) and manual PVI. 17% of patients had SCL immediately after PVI, but all SCL had recovered at 21 months follow up investigation. Factors that may account for divergent findings of SCL after PVI are intra- and periprocedural anticoagulation, activated clotting time, deactivation of the distal and proximal electrode, intraprocedural cardioversion, multiple catheter changes via a single transseptal sheath, and duration of ablation procedures [6,7,12]. In addition, patient related factors such as age and risk of stroke may have an impact on the occurrence of SCL after PVI [6,11,13]. An increased incidence of SCL has been reported for pulmonary vein ablation catheter (PVAC) PVI [1,9,12].

A few studies investigated the occurrence of neuropsychological deficits due to SCL after PVI [8,14,15]. Interestingly, Kochhäuser et al [13] reported a significantly higher number of SCL after PVAC compared to irrigated radiofrequency PVI. Neuropsychological performance was assessed 1 day before, 1 day after and 6 months after ablation. The number of SCL was positively correlated with worse visual and verbal working and long term memory. Moreover, older age negatively influenced neuropsychological performance.

In summary, published data indicate that PVI induces SCL that may sometimes lead to neuropsychological impairments [8,13,14-16]. PVAC PVI is associated with increased incidence of SCL and related neuropsychological impairments compared to other ablation procedures [1,9,14].

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Studies on long term development of SCL after PVI in patients with AF and associated neuropsychological impairments across years are still lacking. The present study therefore addresses this issue by assessing AF patients neuropsychologically and with MRI six to nine years after PVAC PVI. Based on available data, we expected that largeness of frontal lesions positively correlates with severely impaired executive functions, poorer long term memory performance, and deficits in theory of mind (TOM), that older patients have larger frontal lesions than young patients and that AF severity and risk of stroke act as additional risk factors for the incidence of long term neuropsychological deficits after PVAC PVI.

Methods

Sample

20 patients (16 males, 4 females) with AF treated with PVAC PVI (PVAC, Medtronic, Carlsbad, California) in 2009-2012 at Porz am Rhein Hospital were included in data analysis. Inclusion criteria were an age of ≥18<80, native German language skills and normal or corrected eyesight and hearing. Exclusion criteria were additional ablation or cardio version, lesion size in the frontal lobe >70 mm^2 (based on an outlier analysis), IQ<80, BDI>17, chronic neurological or psychiatric conditions, and contraindications for MRI.

Patients were medically and neuropsychologically examined and underwent MRI of the brain. Neuropsychological performance was interpreted with reference to norms of the applied tests and questionnaires. Patients were informed about the aims of the study and the experimental procedures, and written informed consent was obtained. The study complied with the current version of the Declaration of Helsinki and was approved by the ethics committee of Witten/Herdecke University. Demographic and medical data of the sample are summarized in Table 1.

Table 1. Demographic and medical data.

Variable	N
Total	20
Male	16
Female	4
	Mean (SD)
Age (years)	61.00 (8.78)
IQ	10.50 (8.15)
BDI	5.05 (4.17)
CHA2DS2VASc-Score	1.45 (1.32)
EHRA-Classification	2.60 (0.88)
FL cumulated lesion size (mm^2)	14.90 (20.85)

Study design

From 2009-2012, patients with AF were treated with PVAC PVI at Porz am Rhein Hospital. During this time, an MRI of the brain was taken before and after PVI to assess SCL. In the follow up assessment from 2018-2019, patients were again examined medically and underwent MRI to identify the current status of SCL. In addition, a neuropsychological testing battery was applied to examine putative cognitive impairments.

Procedure

MRI: MRI was performed with a 1.5 Tesla scanner (Magnetom Symphony, Siemens, Germany) and evaluated independently by two experienced radiologists (>15 years in the field of neurology). The MRI examination protocol consisted of a T2-weighted axial "fluid-attenuated inversion recovery (FLAIR) sequence" (TI:2200, TR:8150, TE:114 ms; slice thickness 6.0 mm, resolution: 1.3 × 0.9 × 4.0 mm, flip angle:150˚) and a diffusion weighted imaging (DWI) sequence (TR:3700, TE:105, TA:0.13 ms; slice thickness 6.0 mm, resolution: 1.2 × 1.2 × 6.0 mm) with calculation of an apparent diffusion coefficient (ADC) map.

Region of interest analysis of SCL in mm^2 was performed separately for left and right frontal, temporal, parietal, and occipital brain lobes, as well as left and right cerebellum. SCL areas were added across the whole brain and separately for each left and right brain lobe. Given the dominance of frontal lesions and the associated risk for the incidence of severe cognitive dysfunctions, this paper targets only SCL in right, left, and total frontal lobes.

Anamnesis and medical examinations: Medical anamnesis included the status before and the course of disease after PVI, further ablations or cardio versions, medication, and neurological symptoms. An electrocardiogram (ECG) was performed to assess whether the patient was in sinus rhythm. Individual risk of stroke was assessed with the CHA2DS2-VASc-Score. The EHRA classification was used to classify symptoms caused by AF.

Psychological questionnaires: Beck's Depression Inventory II (BDI II) [17] was used to detect current depressive symptoms. The cut off for clinical samples is >17. The State Trait Anxiety Inventory (STAI) [18] was applied to assess state as well as trait anxiety. Dickman's Impulsivity Inventory [19] was used to assess functional and dysfunctional impulsivity.

Neuropsychological assessment: The neuropsychological testing battery included measures of executive functions, memory, attention, TOM, and intelligence. Intelligence was estimated by a short version of the Leistungsprüfsystem 50-Plus [20]. The Reading Mind in the Eyes Test (RMET) [21] was used to measure TOM abilities. It contains 36 pictures each showing the eye area of an adult female or male. 4 emotional adjectives are listed on each picture, with only one adjective matching the emotion expressed by the shown eye pair. The Trail Making Test (TMT) [22] was used to assess visuomotor skills (Part A) and cognitive flexibility (Part B). The HAMASCH 5 point test [23] was additionally applied to assess constructive cognitive flexibility. The word list test of the screening battery of dementia developed by the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) [24] was applied to assess immediate and delayed verbal memory. Results of tests targeting working memory and attention go beyond the scope of this paper and will be reported in a separate article.

Statistical analysis

A Shapiro Wilk Test showed a lack of normal distribution of data. Accordingly, non-parametric statistical tests were applied for statistical calculations. The significance level of all statistical analyses was set to $p<.05$. To assess putative interrelationships between FL lesion size and neuropsychological impairments, Spearman correlations were calculated. Mann-Whitney-U-Tests were applied for group comparisons between young and older patients. For all statistical analyses SPSS 27 (IBM Corp. Armonk, NY) was used.

Results

IQ and clinical symptoms

Patients' mean age was M=61 (SD=8.87). IQ was in the normal range (M=105.5; SD=8.15). None of them showed clinically relevant symptoms of depression according to the BDI-II (M=5.05; SD=4.17). Mean CHA2DS2-VASc-Score was M=1.45 (SD=1.32) and mean EHRA Score M=2.60 (SD=.88).

Neuropsychological data

The sample showed overall declined verbal memory performance. The mean wordlist total score was M=36.47 (SD=25.45), wordlist learning 1 mean score was M=39.73 (SD=19.54), wordlist learning 2 mean score was M=37.29 (SD=24.89), wordlist learning 3 mean score was M=40.37 (SD=20.67), and wordlist delayed recall mean score was M=37.98 (SD=23.08). Scores <37 indicate clinically relevant verbal learning and

memory deficits. The sample did not show deficits in TMT performance (TMT A:M=45.77 (SD=26.75); TMT B:M=44.43 (SD 27.39); scores <37 indicate clinically relevant deficits). The HAMASCH 5 Point Test total mean score was M=51.93 (SD=10.85). Mean score of correct responses was M=52.30 (SD=10.43). In comparison to age matched norms, the patients performed above average in both categories (norms total: M=31.20; SD=10.96; norms correct responses: M=27.54; SD=8.88). For the RMET total, M=23.15 (SD=3.85) correct answers were obtained. Normative values range from 26.2 and 30.9. RMET positive showed a value of M=5.50 (SD=1.36), RMET negative M=7.10 (SD=1.97) and RMET neutral M=10.55 (SD=2.48). Descriptive neuropsychological results are summarized in Table 2.

Table 2. Neuropsychological results.

Neuropsychological Instrument	Min.	Max.	M	SD	Norm
Wordlist learning total	-13.20	66.60	36.47	25.45	<37.00
Wordlist L1	-1.20	66.40	39.73	19.54	<37.00
Wordlist L2	-4.40	67.30	37.29	24.89	<37.00
Wordlist L3	-8.40	62.70	40.37	20.67	<37.00
Wordlist recall	-5.80	62.50	37.98	23.08	<37.00
Trail-making-Test A	-7.20	91.20	45.77	26.75	<37.00
Trail-making-Test B	-8.10	92.80	44.43	27.39	<37.00
5-point test total	37.80	79.30	51.93	10.85	31.20
5-point test correct responses	40.50	84.40	52.30	10.43	27.54
RMET total	17.00	30.00	23.15	3.85	26.2-30.9
RMET positive	3.00	8.00	5.50	1.36	-
RMET negativ	3.00	11.00	7.10	1.97	-
RMET neutral	6.00	15.00	10.55	2.48	-

L=Learning. Min.=Minimum. Max=Maximum. M=Mean. SD=Standard deviation. Wordlist, TMT and 5-Point Test scores are presented as t-values. RMET results are presented as raw values.

MRI data

The extent of SCL showed a high variance. Most lesions were located in the FL. The largest average lesion area was located in the FL (M=14.91 mm^2; SD=20.84), with a comparable extend in the left (M=7.29 mm^2; SD=12.86) and the right FL (M=7.62 mm^2; SD=12.55). In the whole brain, lesion area was M=44.60 mm^2 (SD=62.57). However, only few patients had lesions in the temporal, parietal, and occipital lobes, and the cerebellum. SCL data in the FL are summarized in Table 3.

Table 3. FL lesion areas detected with MRI.

Brain region	Min.	Max.	M	SD	S2
LA left FL	0.00	41.90	7.29	12.86	165.33
LA right FL	0.00	37.10	7.62	12.55	157.51
LA total FL	0.00	64.00	14.91	20.84	434.64

LA=Lesion area (in mm^2). Min.=Minimum. Max=Maximum. M=Mean. SD=Standard deviation. S^2=Variance.

FL lesion size and neuropsychological performance

Significant correlations between the size of FL lesions and neuropsychological performance were found only for verbal memory. Significant negative correlations were found between left FL lesions and Wordlist total (r=-.445*, p=.025), Wordlist learning 1 (r=-.410*, p=.036), Wordlist learning 2 (r=-.529**, p=.008), Wordlist learning 3 (r=-.406*, p=.038), and Wordlist recall (r=-.396*, p=.042). Additionally, there were significant negative correlations between total FL lesions and Wordlist total (r=-.412*, p=.036), Wordlist learning 1 (r=-.441*, p=.026), Wordlist learning 2 (r=.412*, p=.036) and Wordlist recall (r=-.397*, p=.042). The relationship between total FL lesions and Wordlist learning 3 was non-significant (r=-.329, p=.078). There was not any significant effect of right FL lesions on performance of the Wordlist test. Table 4 summarizes correlations between FL lesions and the Wordlist test. Significant results are illustrated in Figure 1.

Table 4. Correlations between FL lesions and the Wordlist test.

	FL left			FL left			FL total		
	n	Corr.	P	n	Corr.	P	n	Corr.	P
Wordlist total	20	-.445*	.025	20	-.187	.215	20	-.412*	.036
Wordlist L1	20	-.410*	.036	20	-.228	.167	20	-.441*	.026
Wordlist L2	20	-.529**	.008	20	-.143	.274	20	-.412*	.036
Wordlist L3	20	-.406*	.038	20	-.116	.312	20	-.329	.078
Wordlist recall	20	-.396*	.042	20	-.189	.213	20	-.397*	.042

Corr.=Spearman correlation coefficient (one-sided). L=learning. *=p .05. **=p<.01.

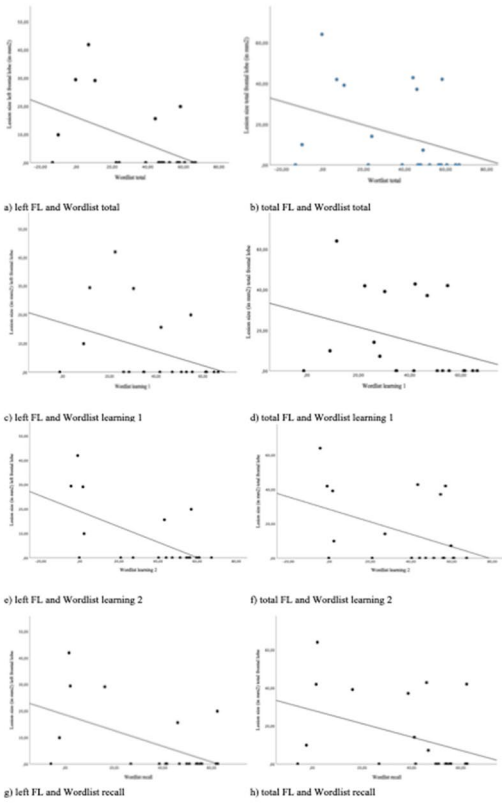

Figure 1. Significant correlations between FL lesions and Wordlist test performance. Test values are presented as t-values

Correlations between lesion size in the left, right, and total FL and the TMT-A (left FL r=-.337, p=.073; right FL r=.062, p=.398; total FL r=-.183, p=.22) and the TMT-B (left FL r=-.33, p=.078; right FL r=.145, p=.271; total FL r=-.155, p=.257) did not reach statistical significance. However, there was a tendency towards statistical significance for left FL and TMT-A

(r=-.337, p=.073) and TMT-B (r=-.33, p=.078). There were no significant correlations of the HAMASCH 5 point test total score and correct responses with lesion size in the left, right, and total FL. There were also no significant correlations between FL lesions and RMET performance.

EHRA classification and neuropsychological performance

Significant positive correlations were found between EHRA and TMT-B (r=.381*, p=.049). All other correlations between EHRA data and neuropsychological performance were non-significant.

CHA2DS2-VASc-Score and neuropsychological performance

Significant negative correlations were detected between CHA2DS2-VASc-Score and TMT-A (r=-.520**, p=.009), TMT-B (r=-.386*, p=.046) and RMET positive (r=-.395*, p=.042). All other correlations between the CHA2DS2-VASc-Score and neuropsychological performance were non-significant. Significant results are illustrated in Figure 2.

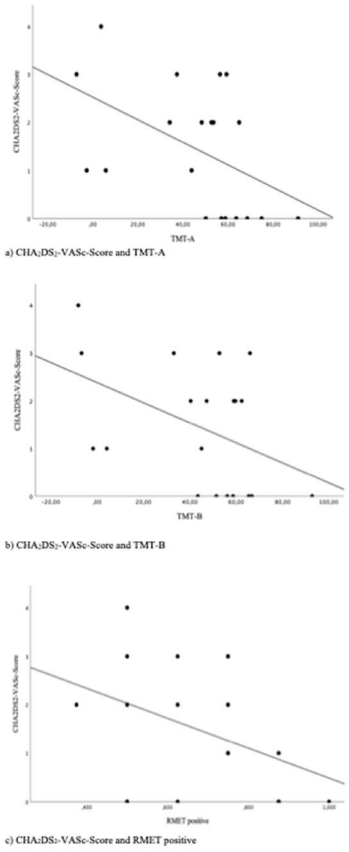

Figure 2. Significant correlations between CHA2DS2-VASc-Score and TMT and RMET performance. TMT-A and TMT-B values are presented as t-values. RMET values are presented as hit rate

Aging effects

A Mann Whitney U Test was calculated to determine whether there were differences in FL lesion size and/or neuropsychological performance in young (n=9; mean age 54 ± 5.17) and older participants (n=11; mean age 66, 73 ± 6.71). There were no statistically significant differences in lesion size in left FL, U=45.000, Z=-.422, p=.766, right FL, U=42.000, Z=-.669, p=.603 or total FL, U=46.000, Z=-.291, p=.824 between age groups. A significant age difference was detected for the number of errors in the d2 [25] test (U=13.500, Z=-2.739, p=.004, r=.61) and the CERAD Mini Mental-Status Test (MMST; U=21.000, Z=-2.165, p=.031, r=.48).

Discussion

The present study investigated the effects of SCL in the FL on neuropsychological performance in AF patients 6-9 years after PVAC PVI. In addition, a putative link between neuropsychological functioning between the risk of stroke and symptom severity of AF was assessed. Largeness of FL lesions positively correlated with poorer verbal memory performance, and there was a statistical trend towards impaired executive functions associated with FL lesions. AF symptom severity negatively affected executive functions. Risk of stroke was associated with executive and TOM dysfunctions. These data demonstrate for the first time evidence for specific persisting long term impairments of memory and executive functions related to SCL in the FL 6-9 years after PVAC PVI.

Data concerning executive dysfunctions after PVI are heterogeneous [8,13-15]. Medi et al [8] showed disturbed executive functions 2 days and 3 months after ablation. MRI was not accomplished. In our study, we found a trend towards a positive correlation between lesion size and persisting diminished performance in TMT-A and B after PVI. These data suggest that SCL in the FL after PVI may induce persisting declines of cognitive flexibility. Comparison with other studies proves to be difficult, as our study is, to the best of our knowledge, the only investigation of cognitive performance after PVI after a period of 6-9 years. Schwarz et al [14] did not find differences in executive functions 3 months after PVI. Bary et al [15] applied the TMT, 1 day before, immediately after and 1 month after ablation. No significant decline in TMT performance was observed, neither immediately, or 1 month after PVI. Moll et al [26] investigated brain activity using fMRI during performance of a virtual version of the TMT in healthy adults. Increased activity related to TMT performance was found in the dorsolateral prefrontal cortex, premotor cortex, left medial frontal cortex, and bilaterally in the intraparietal sulcus. Interestingly, left FL activation was dominant. This finding is in line with our data indicating the strongest statistical tendency for an association between SCL in the left FL and impaired TMT performance. In our study, patients were unimpaired in performance of the HAMASCH 5 point test, which measures visual spatial constructive flexibility, rather than cognitive flexibility and set shifting such as the TMT-B. The data suggest that in our patients SCL in the FL induced selective deficits, but not overall decline of executive functions. This interpretation also fits with the complexity FL functions.

In our study, verbal learning and memory was strongly affected by frontal SCL, with left FL lesions playing the dominant role for impaired performance in both learning and recall trials of wordlist test. The results of Schwarz [14] are consistent with our findings, showing 57% declined performance in verbal memory in AF patients 3 months after PVI. These results could not directly be related to SCL, as all patients showed impaired verbal memory after ablation. Bary et al [15] also reported impaired verbal memory performance in AF patients with SCL 1 month after PVI. Kochhäuser et al [13] demonstrated diminished verbal memory depending dominantly on SCL in the left FL 6 months after PVI. However, in this study SCL were identified by Transcranial Doppler Ultrasound, such that a comparison with our results has limitations.

Overall, published studies show strong evidence that frontal SCL after diverse PVI techniques may cause decline in executive functions and verbal memory. Our data complement available data in that they demonstrate the persistence of these neuropsychological deficits across 6 to 9 years. In contrast to many previous studies, we used MRI to detect SCL and can therefore show a direct link between frontal SCL and selective neuropsychological impairments.

Previous studies of TOM in AF patients after PVI have not been published, yet. In our study, we did not detect any negative effect of SCL in the FL on RMET performance. Nonetheless, it is well known from neuropsychological and functional neuroimaging research that TOM depends to a great extent on the FL [27]. For example, Borbás et al [28] reported increased medial prefrontal as well as orbitofrontal activation during performance of a TOM

task from an fMRI study in healthy humans. Rowe et al [29] showed impaired TOM abilities in patients with unilateral FL lesions. TOM should therefore be assessed with more specific tests than the RMET in AF patients with frontal SCL after PVI, which allow for a differentiation between cognitive and emotional dimensions related to "frontal components" of mind reading.

Published studies suggest that the prevalence of developing SCL after PVI increases with age [13,30]. Our results do not show differences in SCL size in the FL 6-9 years after PVI in younger and older patients. It is likely that this finding is due to the small variance of age in our sample. Moreover, authors who reported age effects on lesion size referred to much shorter time windows after PVI [13,30] than we did in our study. Although FL lesion size did not differ between age groups, older patients performed worse in d2 test of attention and the MMST subtest of the CERAD than young patients. This finding is not surprising since both the d2 test and the CERAD are highly sensitive to aging. The CERAD targets the detection of mild cognitive impairment as a putative precursor of dementia.

In our study, severity of AF negatively affected TMT performance. This finding complements reports of other researchers. For example, Knecht et al [31] showed that AF patients had poorer executive functions, learning and memory performance compared to healthy subjects. Meyre et al [32] demonstrated negative effects of an increased risk of stroke and older age on neuropsychological performance. Our study shows diminished TMT Part A and B as well as RMET (positive emotions) performance related to an increased risk of stroke. Surprisingly, verbal memory was unaffected by risk of stroke, suggesting that selectivity of neuropsychological deficits, which are sensitive to risk of stroke in AF patients after PVAC PVI needs to be further explored.

The results of our study are limited due to the lack of a neuropsychological examination before ablation. Moreover, the sample size is small, and we could not include a group of appropriate control patients in the study. Furthermore, cumulative SCL areas represent rather unspecific descriptions of cerebral lesions. A more specific analysis of SCL is an important next step in research on SCL and neuropsychological decline after PVI methods that are current standards.

Conclusion

Our study is the first providing evidence of neuropsychological long term effects of frontal SCL 6-9 years after PVAC PVI. The data demonstrate poorer verbal memory and a tendency towards impaired executive functions depending on frontal SCL. TOM was not affected by frontal SCL. This finding may indicate that RMET performance does not rely on frontal areas, which are typically damaged after PVAC PVI. In summary, our study emphasizes the importance of combined neuropsychological and MRI assessment of AF patients before, immediately after, and at follow up time points weeks and years after PVI. Note that our data only refer to PVAC PVI, but not to other ablation methods such as IRF and cryoballoon ablation. Moreover, we propose that clinical trials are needed to investigate whether neuropsychological rehabilitation may prevent persisting cognitive long-term deficits in AF patients after PVI.

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Disclosures

The authors disclose any relationships that could be perceived as real or apparent conflicts of interest.

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