ORIGINAL ARTICLE

Functional magnetic resonance imaging for the assessment of autonomic dysfunction in patients with antineutrophil cytoplasmic antibody–associated vasculitides

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KEY WORDS

ANCA-associated vasculitides, antineutrophil cytoplasmic antibodies, autonomic nervous system, functional magnetic resonance imaging, vasculitis

ABSTRACT

INTRODUCTION Nervous system involvement is common in antineutrophil cytoplasmic antibody–associated vasculitides (AAV). While the involvement of the peripheral and central nervous system is well described, it is still unclear how and to what extent the autonomic nervous system (ANS) is affected. Functional magnetic resonance imaging (fMRI) can provide information on both structure and potential damage of the brain, as well as on the function of selected brain centers.

OBJECTIVES The aim of this study was to investigate the ANS dysfunction in AAV patients and its correlation with the results of fMRI performed during the Valsalva maneuver.

PATIENTS AND METHODS A total of 31 patients with AAV and 30 healthy controls were enrolled in the study. Each participant completed the Composite Autonomic Symptom Score (COMPASS)-31 questionnaire. MRI was performed using a 3T scanner. The participants were asked to perform the Valsalva maneuver according to the fixed protocol, and their airway pressure was monitored. During the maneuver, fMRI data were collected. The generalized least-squares time series analysis and the region-of-interest (ROI) analysis were subsequently performed.

RESULTS The patients with AAV had a higher median COMPASS-31 score than the controls (12.86 vs 2.99, respectively; $P < 0.01$). Structural MRI investigation did not reveal any significant differences between the groups. The brain centers involved in ANS function were detected during fMRI; however, the ROI analysis showed no differences between the study patients and controls.

CONCLUSIONS The patients with AAV reported symptoms related to the ANS dysfunction; however, no differences with respect to the functioning of the ANS brain centers were demonstrated between these patients and healthy controls in the fMRI study during the Valsalva maneuver.

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Received: May 5, 2023.
Revision accepted: July 11, 2023.
Published online: July 14, 2023.
Pol Arch Intern Med. 2023; 133 (12): 16533
doi:10.20452/pamw.16533

INTRODUCTION Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) affect various body systems. They are most often manifested by respiratory, renal, as well as ears, nose, and throat (ENT) symptoms.[1] Nervous system involvement is also common.[2,3] AAV most often affect the peripheral somatic nervous system.[4] This type of manifestation occurs in all AAV subgroups with varying prevalence, and is relatively well described. Less frequently, the disease affects the central nervous system,[5,6] which is usually associated with worse prognosis.[5]

WHAT'S NEW?

The prevalence and extent of autonomic nervous system (ANS) dysfunction in patients with antineutrophil cytoplasmic antibody–associated vasculitides (AAV) have not been fully investigated. In this study, we assessed the autonomic dysfunction in patients with AAV and healthy controls. The former group had significantly higher Composite Autonomic Symptom Score-31 values. Functional magnetic resonance imagining during the Valsalva maneuver was used to assess activation of the ANS centers in the brain. The results showed that AAV patients had the same central ANS function as the controls. This can indicate that the symptoms of ANS dysfunction in AAV may result from peripheral ANS damage.

In contrast, involvement of the autonomic nervous system (ANS) remains unclear.[7] There are several methods to assess the autonomic dysfunction. The presence of symptoms and their severity can be assessed using a self-administered questionnaire—the Composite Autonomic Symptom Score (COMPASS)-31.[8] It is a well-researched tool, validated in numerous diseases, including small fiber polyneuropathy,[9] autoimmune diseases, such as scleroderma,[10] and systemic vasculitis.[11,12]

Various ANS testing tools have been used to assess autonomic dysfunction in patients with AAV, including heart rate variability,[13] blood pressure response to pain, skin conductance changes during mental arithmetic tasks, and dynamic pupillometry,[11,12] but the results were inconclusive.

Another well-known ANS test is the Valsalva maneuver. It consists in maintaining an increased intrathoracic pressure, which, by activating reflexes from the ANS, causes well-described, measurable hemodynamic changes.

Functional magnetic resonance imaging (fMRI) seems to be a promising method to assess ANS functioning.[14] It is possible that changes in the nervous system caused by systemic vasculitis result from damage to small vessels, and thus the affected areas may be limited and inaccessible to typical structural MRI.[15,16] However, from the clinical point of view, the most important thing is to assess the functioning of the nervous system. In this context, fMRI may help establish whether the ANS function is disturbed at the central level.

Following the studies on chronic fatigue syndrome by He et al,[17] Bohr et al,[18] and Vuong et al,[14] which have demonstrated the usefulness of fMRI during the Valsalva maneuver, we decided to investigate the utility of this method in patients with AAV.

The aim of this study was to assess the ANS dysfunction in patients with AAV and its correlation with the results of fMRI performed during the Valsalva maneuver.

PATIENTS AND METHODS

Patients A total of 31 consecutive patients with AAV treated at a single tertiary center were enrolled in the study. The inclusion criteria comprised the diagnosis of AAV with the presence of antibodies against myeloperoxidase (anti-MPO) or proteinase 3 (anti-PR3), no disease activity, defined as 0 points in the Birmingham Vasculitis Activity Score, version 3 (BVAS v.3),[19] and age between 18 and 70 years. We excluded the patients with comorbid conditions potentially affecting the nervous system, such as diabetes mellitus, uncontrolled thyroid disorders, or chronic kidney disease (stage 3 or higher), patients on medications, such as β-blockers, rate-controlling calcium channel blockers, or tricyclic antidepressants, and those with contraindications to MRI of the head (eg, metallic implants, artificial heart valves, vascular clips, and other potentially ferromagnetic foreign bodies, claustrophobia, pacemakers, neurostimulators, and other biostimulators). One patient enrolled in the study did not finally undergo fMRI due to significant anxiety.

The control group consisted of 30 healthy volunteers who matched the study group in terms of age and sex. Each participant provided a written informed consent. The study was conducted in accordance with the Declaration of Helsinki. It was reviewed and approved by the Bioethics Committee of the Jagiellonian University (KBET/286/B/2012). Demographic and medical history data were collected from the available medical records.

Autonomic symptoms questionnaire Each participant was asked to complete the COMPASS-31 questionnaire, which consists of 31 questions grouped into 6 domains: orthostatic, vasomotor, secretomotor, gastrointestinal, urinary, and pupillomotor. The score for each domain was weighted according to the previously described methodology[8]; then, all the scores were added to give a total score ranging from 0 to 100 points.

Magnetic resonance imaging data acquisition MRI was performed using a 3T scanner with a 32-channel head coil (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany).

The procedure was divided into 2 stages. In the first stage, anatomical scans were performed. Subsequently, fMRI was carried out during the Valsalva maneuver.

High-resolution, whole-brain anatomical images were acquired using TSE T2, FLAIR, and SWI3D sequences with respective transverse slices of 1.5, 3, and 5 mm, as well as with SPC T2 and T1 MPRAGE sequences in 0.9-mm sagittal slices. For the T1 MPRAGE scan, a total of 176 sagittal slices were obtained (voxel size, 0.94 mm^3; matrix size, 256 × 256; field-of-view [FOV], 240 mm × 240 mm; repetition time [TR], 2300 ms; echo time [TE], 2.29 ms; flip angle, 8 °). Then, the scans were transferred to and analyzed by an experienced radiologist, who was blinded to the participant data.

For functional data acquisition, the gradient-echo EPI sequence was used. During the task sequence, 155 volumes, each consisting of 47 axial

slices, were acquired with the following parameters: TR, 2500 ms; TE, 27 ms; 3-mm isotropic voxel, flip angle, 90 °; FOV, 192 mm × 192 mm, GRAPPA acceleration factor 2. The task sequence was followed by a resting-state sequence with the same scan parameters, lasting approximately 10 minutes (240 measurements). The first 4 volumes (dummy scans) were discarded from the analysis due to the magnetic saturation effect. A gradient fieldmap was obtained with the same geometric parameters.

Physiological data were collected using a scanner-compatible electrocardiogram, a respiratory belt placed around the abdomen, and a pulse-oximeter placed on the index finger of the left hand.

Valsalva maneuver To apply the Valsalva maneuver in a comparable way in each patient, it was conducted according to the protocol based on the previous studies by He et al[17] and Bohr et al.[18] Each patient was asked to perform the Valsalva maneuver 6 times during the fMRI procedure. The task was explained in detail to each participant and a preprocedural trial was conducted. The visual aid was prepared and generated using E–Prime 2.0 software (Psychology Software Tools, Pittsburgh, Pennsylvania, United States). It was presented on a 32-inch screen located behind the MRI scanner and approximately 100 cm from the head coil. The participants were able to see the screen using a single mirror placed on the head coil.

The single Valsalva maneuver lasted 1 minute and consisted in a 16-second forceful exhalation against a single-use plastic tube with an antimicrobial filter, connected to a custom-made pressure sensor located outside the MRI scanner room (Ober-Consulting, Poznań, Poland). Task performance feedback was displayed to the patient graphically in the form of a grey bar changing its length proportionally to the pressure load, and switching its color to green once a threshold of 35 mm Hg for women and 40 mm Hg for men was achieved. The participants were asked to achieve the threshold in the shortest possible time. Following termination of the forceful expiration, a 44-second rest period ensued, and the instruction "Breathe peacefully through your nose" was displayed on the screen. The participants were asked not to remove the plastic tube from their mouth between the maneuver attempts and not to use their hands as support for the tube.

Functional magnetic resonance imaging analysis Preprocessing of the fMRI data was performed using the Analysis of Functional NeuroImage (version 17.3.03)[20] and the FMRIB Software Library (FSL; version 5.0.9).[21] Anatomical images were skull-stripped (3dSkullStrip) and coregistered to the Montreal Neurological Institute (MNI) space using nonlinear transformation (3dQWarp). The cerebrospinal fluid (CSF) mask was created using a segmentation procedure (3dSeg). The functional data preprocessing started with despiking (3dDespike) and slice timing correction (3dTshift); subsequently, motion (3dvolreg) and image distortion (Fugue, FSL) corrections were performed. After coregistration to the skull-stripped anatomical images, the functional images were coregistered to the MNI space using the transformation matrix from nonlinear anatomical normalization. Then, the images were rescaled to represent the percent signal change, and the time course of CSF was extracted. Finally, functional data were detrended and the CSF signal was regressed out.

Data from 3 participants were discarded from further analysis (due to technical issues—missing task performance data [n =1] or invalid task performance [n = 2]).

The generalized least-squares time series analysis with the prewhitening option (3dREMLfit) was performed using the model that included 6 movement parameters and 3 task regressors: the Valsalva maneuver modeled as the 16-second block and cue, and the rest onset modeled as the event. As a result, the map of activity during the task was generated. Subsequently, the comparison between the patients and controls was performed using the *t* test.

The region-of-interest (ROI) analysis was performed using a mask generated from the Harvard–Oxford subcortical atlas. The time course was extracted from preprocessed data and 30-second epochs were averaged across correct trials for each participant, and then across participants for both groups.

Statistical analysis Standard descriptive statistics were used. The normality of distribution of variables was checked with the Shapiro–Wilk test. To compare the 2 groups, the χ^2 test (with Yates correction, if needed) for dichotomous variables and the Mann–Whitney test for continuous variables were used. A *P* value below 0.05 was assumed as significant. Calculations were performed with StatSoft Statistica 13 software (StatSoft, Tulsa, Oklahoma, United States).

RESULTS

Patient characteristics A total of 31 patients (12 women, 19 men) were included in the study group. Of those, 25 had anti-PR3 antibodies and 6 had anti-MPO antibodies. The most prevalent organs involved were the respiratory system, kidneys, and ENT. All patients were treated with steroids and most of them also with cyclophosphamide during the remission induction phase. The most frequent comorbidities were arterial hypertension, hypothyroidism, and secondary immune deficiency.

The control group consisted of 30 sex- and age-matched individuals (12 women, 18 men). Six of them had a history of arterial hypertension.

The general characteristics of the AAV cohort and a comparison of selected parameters between the AAV patients and controls are

TABLE 1 General characteristics of the AAV group and comparison of selected parameters between the AAV patients and controls

Parameter	AAV group (n = 31)	Control group (n = 30)
General characteristics		
GPA	25 (80.6)	–
MPA	4 (12.9)	–
EGPA	2 (6.5)	–
Age, y, mean (SD)	44 (15.3)	44.6 (15.3)
Women	12 (38.7)	12 (40)
Time from diagnosis to MRI, y, median (IQR)	2 (1–5)	–
Organ involvement		
ENT	17 (54.8)	–
Respiratory system	26 (83.9)	–
Eye	3 (9.7)	–
Kidneys	19 (61.3)	–
Musculoskeletal system	9 (29)	–
Skin	11 (35.5)	–
Nervous system	9 (29)	–
Gastrointestinal system	1 (3.2)	–
Heart	0	–
Treatment		
Steroids	31 (100)	–
Cyclophosphamide[a]	29 (96.7)	–
Cyclophosphamide cumulative dose, g, median (IQR)	9.5 (7–16.1)	–
Azathioprine	8 (25.8)	–
Rituximab	14 (45.2)	–
Comorbidities[b]		
Arterial hypertension	10 (32.2)	6 (20)
Hypothyroidism	3 (9.7)	0
Secondary immune deficiency	3 (9.7)	0
Bronchial asthma	2 (6.5)	0
Venous thromboembolic disease	2 (6.5)	0

Data are presented as number (percentage) of patients unless indicated otherwise.

a No data for 1 patient

b Comorbidities present in at least 2 patients were reported.

Abbreviations: AAV, antineutrophil cytoplasmic antibody–associated vasciuitides; EGPA, eosinophilic granulomatosis with polyangiitis; ENT, ears, nose, and throat; GPA, granulomatosis with polyangiitis; IQR, interquartile range; MPA, microscopic polyangiitis; MRI, magnetic resonance imaging

presented in TABLE 1. Previous cerebral ischemic stroke and cerebral hemorrhage were reported by 1 AAV patient each. None of the controls reported a cerebral episode.

Autonomic dysfunction symptoms The patients with AAV had a higher median (interquartile range [IQR]) COMPASS-31 score than the controls (12.86 [4.45–23.91] vs 2.99 [0–7.12], respectively; P <0.01). The patients with nervous system involvement did not show a higher COMPASS-31 score than those without such symptoms (median [IQR], 15.73 [6.73–26.02] vs 10.96 [4.45–18.28], respectively; P = 0.71).

Structural magnetic resonance imaging Structural MRI findings are presented in TABLE 2. The most frequently reported changes in the brain area were nonspecific white matter lesions (WMLs) in various locations. They were found in half of the study group and in half of the controls. In both groups, 20% (3/15) of the abnormalities were described as numerous or moderate. Arterial hypertension was present in 40% (6/15) of the AAV patients with WMLs, and 40% of the controls.

In the AAV group, the radiological signs of sinusitis were more common than in the controls (80% vs 50%, respectively; P = 0.03), with severe sinus involvement present only in the AAV group.

Valsalva maneuver Overall, 2 out of 60 participants did not perform the task correctly, that is, they did not reach the threshold level of pressure. The rest of the participants performed the task with 82% accuracy—almost 5 of 6 Valsalva trials were correct. There was no difference in the task performance between the study patients and controls (P = 0.14).

Functional magnetic resonance imaging results The generalized least-squares analysis revealed several clusters activated during the Valsalva maneuver (P <0.001; t >4.6): the right intraparietal sulcus, right middle temporal gyrus, right superior temporal gyrus, right hippocampus (partially including the amygdala), left thalamus, bilateral motor and sensory cortices, bilateral putamen, as well as the cerebellum and brainstem. Detailed information is provided in TABLE 3 and FIGURE 1.

The ROI analysis was performed for the bilateral amygdala, putamen, and pallidum clusters. The results are presented in FIGURES 2 and 3. There were no differences between the AAV group and the control group.

DISCUSSION Our study found greater involvement of the ANS in the AAV group than in the control group, as demonstrated by significantly higher COMPASS-31 scores. This tool has already been used to assess patients with AAV, and the results obtained in the current study (12.86 vs 2.99 points) are consistent with previous reports (10.4 vs 3 points).[11]

fMRI allows for a comprehensive brain assessment, both structural and functional. Structural MRI investigation did not reveal any significant differences between the groups. The most common MRI findings (WMLs) were present with the same frequency in the study patients and the healthy controls (50% in each group). Interestingly, in a study using MRI in patients with AAV during the disease exacerbation, WMLs were detected in almost all participants (94.4%).[22] Unfortunately, methodological differences do not allow for a direct comparison of the results. In our study, WMLs were assessed in the T2 and FLAIR sequences, and the authors of the mentioned study used also the SWAN technique, which they found significantly better than

TABLE 2 Head structural magnetic resonance imaging findings

Parameter	AAV group (n = 30)[a]	Control group (n = 30)
White matter lesions	12 (40)	12 (40)
Numerous white matter lesions	3 (10)	3 (10)
Past cerebral infarction	4 (13)	1 (3)
Past cerebral hemorrhage	1 (3)	0
Hemosiderin deposits	2 (6)	3 (10)
Sinusitis (mild)	14 (47)	14 (47)
Sinusitis (severe)	5 (17)	1 (3)
Sinusitis with bone destruction and remodeling	5 (17)	0
Other minor findings	5 (17)[b]	7 (23)[c]

Data are presented as number (percentage) of patients.

a One patient enrolled in the study did not undergo the MRI procedure.

b Pineal cyst, arachnoid cyst, microaneurysm, venous malformation

c Pineal cyst, arachnoid cyst, Rathke cleft cyst, ecchordosis physaliphora, microaneurysm

Abbreviations: see **TABLE 1**

TABLE 3 Clusters of activity related to the Valsalva maneuver

Cluster	Side	Voxels, n	Center of mass coordinates		
			x	y	z
Inferior parietal lobe	Right	365	–36.7	+59.2	+40.3
Cerebellum, lobule V	Right	256	–3.2	+53.7	–23.1
Putamen	Right	254	–30.1	+9	+5.5
	Left	167	+28.1	+11.6	+5.7
Thalamus	Right and left	191	–3.7	+17.7	+1.6
Middle temporal gyrus	Right	89	–47	+63.9	+1.8
Superior temporal gyrus	Right	38	–50.4	+42.5	+12.3
Postcentral gyrus	Right	85	–48.3	+13.1	+34.4
	Left	34	+42.1	+15.6	+35.2
Inferior frontal gyrus	Right	64	–44.2	–8	+27.5
Precentral gyrus	Right	33	–34.1	+2	+49.9
Middle cingulate cortex	Left	42	+10.4	+20.8	+38.5
	Right	31	–13	+28.1	+38
Hippocampus	Right	33	–29	+12.3	–22
Brainstem	Right	30	–1.8	+26.2	–21.2

FLAIR for WML detection. Moreover, the cited study included a slightly different group of patients—all of them had kidney involvement, whereas in our study, renal manifestation affected 61.3% of the patients.

To our best knowledge, this is the first study using fMRI to investigate autonomic dysfunction in patients with AAV. The results confirmed a preserved activation of the brain regions previously described in fMRI studies performed during the Valsalva maneuver.[14,17,23] In order to exclude the influence of acute inflammation on ANS functioning,[24] we only included AAV patients in remission (BVAS v.3 of 0). However, the ROI analysis showed no differences between the study patients and healthy controls. This may mean that the autonomic centers activated during the Valsalva maneuver are not damaged in the course of AAV. The more frequently reported autonomic symptoms in AAV patients may result from damage to the peripheral part of the ANS. This would be consistent with the general tendency that in AAV the peripheral nervous system is more frequently involved than the central one. Alternatively, the observed differences were too discrete to be demonstrated with our study sample. On the other hand, studies conducted so far, using methods such as skin conduction or pupillometry,[11,12] did not demonstrate ANS damage in AAV patients. However, this could be explained by the application of methods limited to single aspects of the ANS, such as sudomotor or pupillary function. Application of the COMPASS-31 questionnaire allowed us to assess a much broader spectrum of the autonomic symptoms and—although not involving any physiologic measurements—provided a comprehensive evaluation of nearly all aspects of ANS functioning in our study participants, thus demonstrating even the subtle differences characterizing the AAV patients. Some other factors that may have influenced the observed higher incidence of ANS symptoms in our patients include the effects of drugs that could mimic these types of symptoms (eg, steroids causing excessive sweating or blood pressure imbalance).

Clinically, the application of fMRI in AAV patients may also be relevant as an additional tool to evaluate the potential involvement of the central nervous system in AAV, as the preserved integrity of the central autonomic network is crucial both for adequate bodily responses to various everyday events (eg, physical effort, orthostatic stress, or emotions) and for survival in general. Indeed, involvement of the central nervous system in AAV has been shown to be associated with worse prognosis.[5] Even if there is no causal treatment, just being aware of such disorders can improve our understanding of the symptoms reported by the patients and encourage closer monitoring of other risk factors that contribute to, for example, increased cardiovascular risk. Certainly, fMRI is quite a complicated procedure, often difficult to interpret, and—unlike structural MRI—it cannot be used as a routine evaluation. However, in specific cases, such as in patients with autonomic dysfunction confirmed by standard tests, fMRI could be used to determine whether central ANS is also involved. Furthermore, considering the universal involvement of the white matter in AAV during exacerbation of the disease,[22] fMRI might be useful in detecting even transient changes in the functioning of the central ANS associated with temporary regional reduction of cerebral blood flow. However, to better determine the usefulness of fMRI in such a setting, studies involving patients during exacerbation of AAV are warranted. Nonetheless, given the very limited number of specific tests

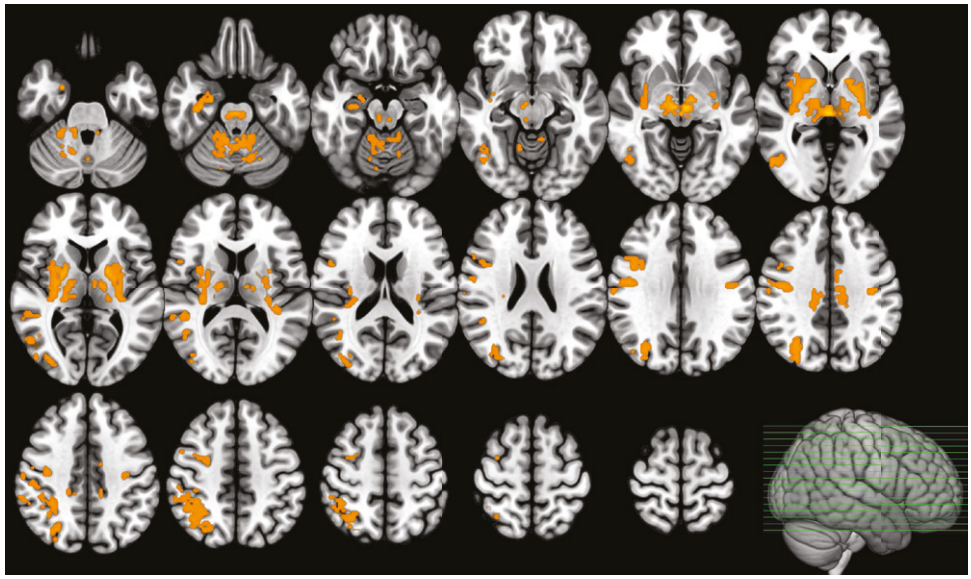

FIGURE 1 Location of the activated clusters related to the Valsalva maneuver

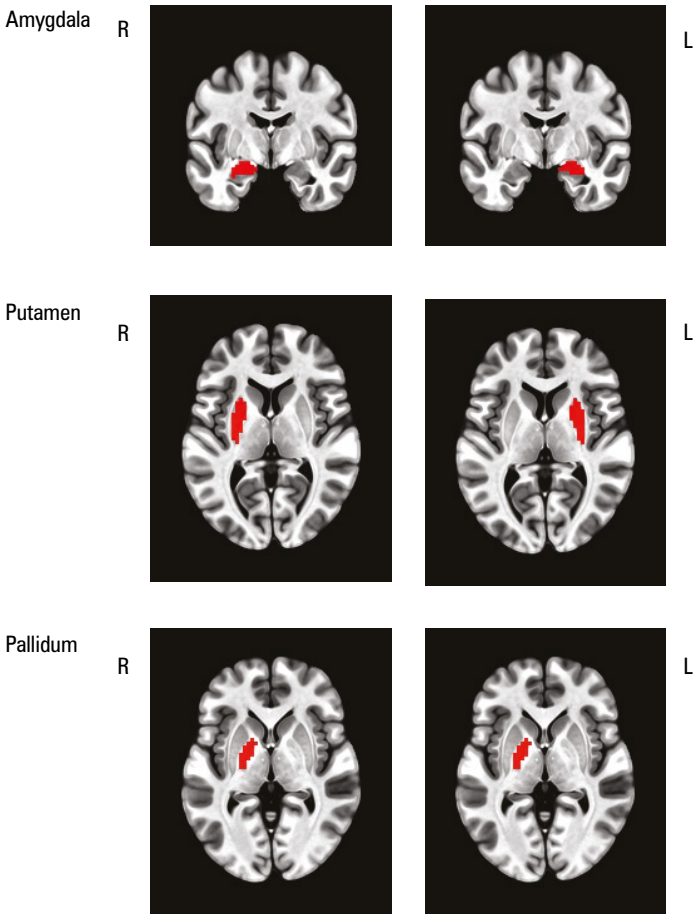

FIGURE 2 Localization of the regions of interest
Abbreviations: L, left; R, right

differentiating postganglionic and preganglionic ANS involvement (eg, the quantitative sudomotor axon reflex test or cardiac ^{123}I-metaiodobenzylguanidine scintigraphy, both primarily detecting postganglionic damage),[25] fMRI seems to be a promising tool to determine the function of specific structures within the central autonomic network in various other autonomic disorders, such as those associated with diabetes, multiple sclerosis, multisystem atrophy, Parkinson disease, and others.

The present study has several limitations. During the Valsalva maneuver, continuous blood pressure measurement was not possible due to MRI properties and safety-related hardware limitations. Moreover, heart rate measurements were severely affected by electromagnetic waves (noise), thus preventing analysis of these data in terms of heart rate variability. Therefore, no continuous blood pressure or heart rate changes data were obtained that could directly prove the function of the peripheral ANS. On the other hand, in the absence of continuous blood pressure monitoring, the occurrence of phase IV of the maneuver (blood pressure overshoot following cessation of the forced expiration) cannot be confirmed, while this overshoot is essential to induce baroreflex-mediated heart slowing immediately following the blood pressure increase.[26] Therefore, it is not recommended to interpret the vagally-mediated heart rate responses to the Valsalva maneuver without the accompanying continuous blood pressure monitoring and demonstration of the presence of the phase IV–associated blood pressure overshoot. However, we precisely monitored the intrathoracic pressure during the Valsalva maneuver in our study participants; thus, we were able to confirm if the maneuver had been performed correctly.

Conclusion Patients with AAV experience symptoms related to the ANS dysfunction more often than healthy individuals; however, no differences in the functioning of the brain centers responsible for the ANS have been demonstrated based on fMRI performed during the Valsalva maneuver. Symptoms of ANS dysfunction in AAV are more likely to originate from peripheral nerve damage, because central autonomic control is preserved. Further studies investigating the nature of the autonomic symptoms are needed.

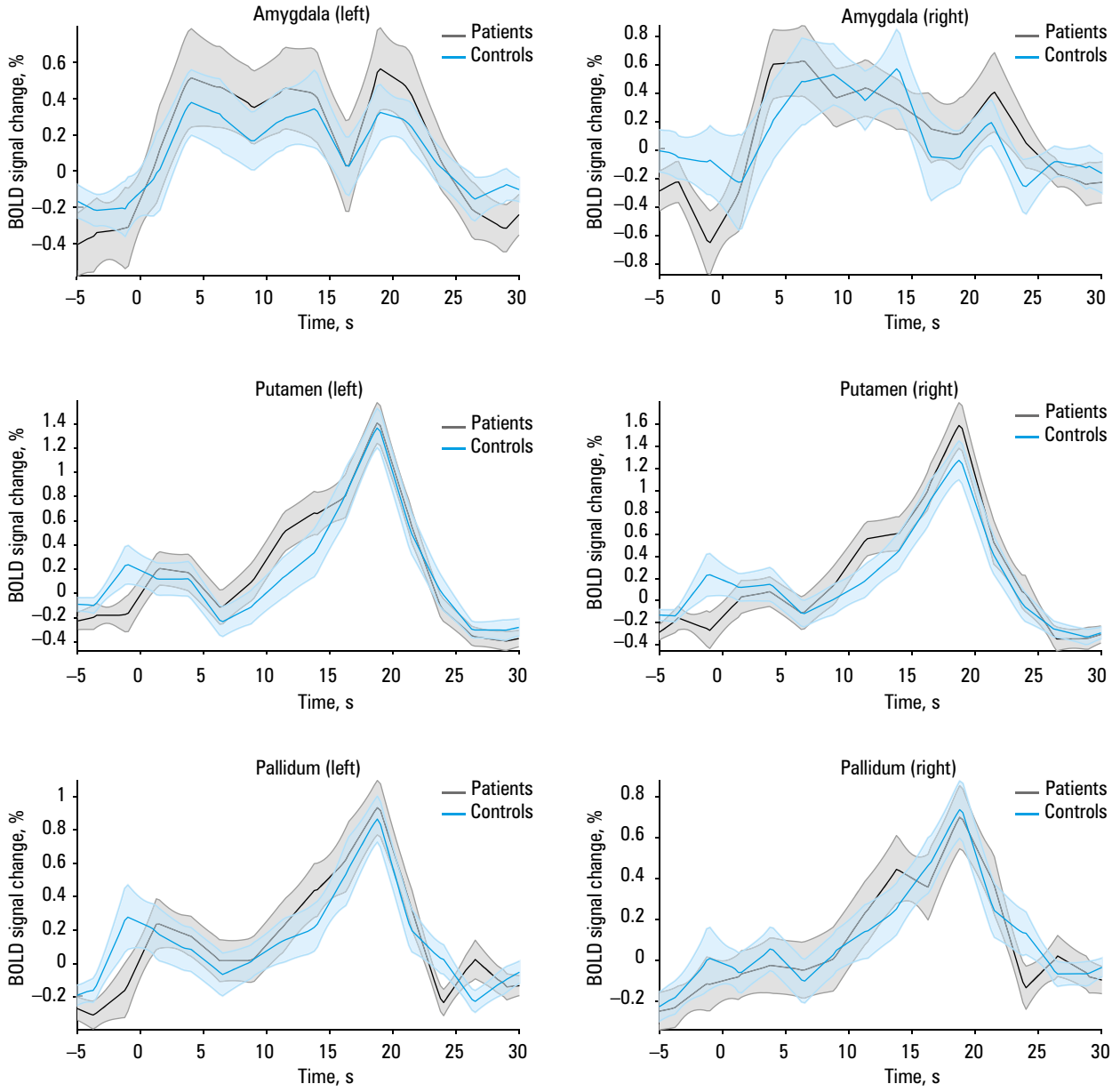

FIGURE 3 Results of the region-of-interest analysis (based on the Harvard–Oxford atlas); 0 seconds on the X axis refers to the start of the Valsalva maneuver

Abbreviations: BOLD, blood oxygen level–dependent

ARTICLE INFORMATION

ACKNOWLEDGMENTS We thank Monika Ostrogórska (Department of Radiology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland) and Adrian Tymorek (Faculty of Biology, Jagiellonian University, Kraków, Poland) for their invaluable help in conducting the fMRI procedures.

FUNDING This work was supported by the Polish National Science Centre (NCN) (2013/11/N/NZ5/00022; to AW).

CONTRIBUTION STATEMENT AW and WS conceived the idea for the study. MT, AD, and TM contributed to the design of the research. AW, GB, KW-A, and AD were involved in data collection. AW, AD, PŁ, and MT analyzed the data. AW, AD, and GB prepared the main body of the manuscript. MT, KWA, and JS provided expert opinions and corrections. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Wludarczyk A, Domagalik A, Biedroń G, et al. Functional magnetic resonance imaging for the assessment of autonomic dysfunction in patients with antineutrophil cytoplasmic antibody–associated vasculitides. Pol Arch Intern Med. 2023; 133: 16533. doi:10.20452/pamw.16533

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