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Executive self-control in patients with arterial hypertension – cognitive and neuroimaging parameters measured with selected neuropsychological tests and fMRI

***Abstract**: Background: Arterial hypertension (HTN) ranks among the most widespread chronic illnesses that affect adults in industrialized societies. The main goal of this study was to describe the control (inhibition) processes among HTN patients, and to evaluate the dynamics of brain activity while the patients were engaged in tasks measuring the cognitive aspect of self-control.*
Participants and procedure: A set of neuropsychological tests (California Verbal Learning Test, Color Trails Test, The Trail Making Test, Controlled Oral Word Association Test), and a fMRI Stroop test (rapid event design) were administered to 40 persons (20 HTN patients and 20 controls). Groups were matched in terms of age, sex, education, smoking history, and waist-to-hip ratio.
Results: As revealed by fMRI, the HTN patients demonstrate left-hemisphere asymmetry in inhibitory processes. Also around 90% of patients had problems when completing tasks which rely on verbal and graphomotor aspects of self-control.
Conclusions: The results suggest that both cerebral hemispheres must interact correctly in order to provide successful executive control. The deficiencies in control and executive functioning, which were observed among the patients, prove that HTN negatively affects brain processes that control one's cognitive activity.

***Keywords**: hypertension, executive functions, functional magnetic resonance imaging, neuropsychological evaluation*

Introduction

With over 68 million people worldwide suffering from it, arterial hypertension (HTN) is one of the most widespread illnesses among adults in industrialized societies (according to the report by the National Center for Chronic Disease Prevention and Health Promotion, CDC 2011). The epidemiology of HTN is closely linked to the patients' age and sex. Every ten years of one's life increase the risk of HTN by 10%, and in the population of individuals aged 65+ the prevalence of HTN may reach 60–70% (cf. Witkowska, Naumczyk, Jodzio, 2015). Arterial

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hypertension occurs when blood pressure is excessively elevated due to unspecified or ambiguous causes. There are two basic types of this disease: primary high blood pressure (without a known somatic cause) and secondary high blood pressure (HTN occurring as a symptom of another, primary somatic disease) (cf. Luban-Plozza et al., 1995; Wierucki et al., 2004; Moryś et al., 2005).

Particularly the neuropsychological consequences of arterial hypertension deserve our attention. The changes to the vascular system lead to numerous (both immediate and long-term) pathologies of cerebral circulation (Kuo et al., 2005), which in turn increase the risk of a cerebrovascular accident, etc. (Bobrie et al., 2008; Verberk, Kessels, de Leeuw, 2008). Researchers emphasize that the frontal lobes (Raz, Rodrigue, Acker, 2003; Sizova et al., 2018) and white matter (Bryan et al., 2009; Krukow, 2014; Suzuki et at., 2017) are particularly susceptible to damage as a result of (intra)cerebral hemorrhage triggered by HTN. Other often cited neuropsychological problems associated with HTN include: general deterioration of one's cognitive functions (Sizova et al., 2018) and executive dysfunctions (Hajjar et al., 2014), which result from either attention span deficits (Li et al., 2015) or disorders that affect the use of control processes (Chuang et al., 2014); speech, thinking, and memory remain relatively intact (Seo et al., 2007; Werring et al., 2010; Hajjar et al., 2014).

Hanon (2005) stated that cognitive abilities in one's senior years correlate negatively with HTN diagnosed 15 or even 20 years earlier. Initially, high blood pressure disturbs microcirculation and increases the production of amyloid protein. Consequently, lesions develop in brain's blood vessels, most likely causing disorders across the spectrum of cerebral small vessel diseases – namely cerebral microbleeds (CMB) and cerebral microinfarcts (CMI). Next, white matter and gray matter are damaged (cortical lesions), and various dementia symptoms occur; these may be of vascular type (vascular dementia, VaD), Alzheimer type (Alzheimer's disease, AD), or in the form of vascular cognitive impairment (Opala, Ochudło, 2004; Zabłocki, Leszek, 2006; Nyenhuis, 2014). The last group encompasses many diverse vascular mental or cognitive disorders, which result from selective atrophy of cortical and subcortical regions, most often located in the brain's frontal lobes (Witkowska, Naumczyk, Jodzio, 2015; Sizova et al., 2018).

After reviewing a body of literature on the subject, we noticed that researchers tend to focus on traditional psychosomatic aspects of the illness – such as emotions or stress – and neglect potential cognitive consequences of HTN. The functioning of the central nervous system is examined solely in relation to brain vascular diseases. Consequently, the detrimental impact of HTN on the functioning of the central nervous system, and the premature aging processes in the brain expressed as vascular-related cognitive deficits, are often marginalized. This is why an early neuropsychological diagnosis of HTN patients becomes vital.

The main goal of this study was to describe the control (inhibition) processes, of selected cognitive functions among HTN patients, and to evaluate the dynamics of brain activity while the patients were engaged in problem-solving tasks of the cognitive aspect of self-control.

Participants and Procedure

Initially, 90 persons were examined using neuropsychological tests, standard MRI of the brain, and functional MRI. The procedures followed were in accordance with the ethical standards of the bioethical committee on human experimentation. Patients gave their informed consent to participating in the whole project. Individuals diagnosed with neurological disorders (e.g., ischemic stroke, meningitis), psychological and somatic disorders, whose treatment could negatively affect one's central nervous system (e.g., chemotherapy); and all cases of MRI artifacts, were excluded from further research. Final group consisted of 40 right-handed persons, including 20 patients with primary arterial hypertension (the criterion group) and 20 volunteers who formed the control group. Every person in one group had a matching individual in the other group, characterized by the same age, sex, education level (based on the number of school years completed), smoking history, and WHR. The analysis was then performed using Student's *t*-test for independent samples. Participants from the criterion group were patients of the hospitals' Regional Center of Hypertension and were well reacting to standard HTN treatment.

The diagnosis of hypertension was based on the European Society of Hypertension/European Society of Cardiology criteria (Mancia et al., 2013). Twenty-four hour ambulatory blood pressure monitoring (ABPM) was used on every subject to confirm blood pressure status. ABPM was performed within 3 weeks following a functional MRI study with the Spacelabs 90207 recorder (Spacelabs Inc.). The recorders were programmed to obtain measurements every 20 minutes from 6:00 AM to 10:00 PM (day), and every 30 minutes from 10:00 PM to 6:00 AM (night). Office blood pressure was assessed at the day of the functional MRI study.

In the HTN group, mean time from the diagnosis of hypertension was 10.7 ± 9.4 years. Patients were treated with ACE inhibitors (45%), Angiotensin II receptor antagonists (30%), calcium channel blockers (35%), diuretics (40%), *β*-blockers (25%), and α-blockers (10%). Mean number of antihypertensive drugs was 1.85 (median value 2.0). Lipid-lowering drugs (statins) were used in 35% of patients and 20% of controls. Table 1 presents basic demographic and medical data.

Neuropsychological assessment of the examined participants

We employed a set of standardized psychological tests to examine the participants' mnestic, linguistic, and executive functions. The ability to learn and recall verbal material was examined with the California Verbal Learning Test (CVLT; r_{tt} .9–.94; Łojek, Stańczak, 2010). To assess various processes connected with attention and executive

Table 1. Selected demographic and medical characteristics of the examined participants

	Criterion group (n = 20)	Control group (n = 20)	*t*-test	*p*
Age (in years)[1]	48.9 (8)	45.4 (11.4)	1.12	.27
Number of school years[1]	14.8 (2.6)	16.4 (3.1)	–1.75	.09
Males/Females[2]	11 (55%) /9 (45%)	11 (55%) /9 (45%)	–	–
Cigarette smoking:				
– number of pack-years[1]	6.4 (9.7)	6.1 (9.2)	.12	.9
– currently[2]	3 (15%)	4 (20%)	–	–
– in the past[2]	6 (30%)	5 (25%)	–	–
– never[2]	11 (55%)	11 (55%)	–	–
Body Mass Index [kg/m2]	31.6 (6.4)	26.5 (2.8)	-3.25	.002*
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.05)	–1.51	.13
Systolic blood pressure [mmHg]:				
– Office	131.0 (12.7)	124.5 (9.8)	–1.83	.07°
– Ambulatory daytime	130.3 (9.8)	123.3 (9.3)	–2.32	.02**
– Ambulatory nighttime	114.1 (9.6)	109.3 (8.0)	–1.70	.09
Diastolic blood pressure [mmHg]:				
– Office	84.4 (7.8)	77.3 (7.8)	–2.87	.006*
– Ambulatory daytime	82.7 (9.9)	78.2 (4.7)	–1.86	.07°
– Ambulatory nighttime	69.2 (9.7)	65.7 (5.7)	–1.39	.17
Cholesterol:				
– Total [mg/dl]	203.6 (44.8)	214.2 (43)	.76	.45
– LDL [mg/dl]	123.8 (36.2)	135.3 (42.8)	.90	.37
– HDL [mg/dl]	53.5 (14)	54.4 (19.1)	.18	.86
Triglycerides [mg/dl]	131.1 (67.7)	122.7 (92.3)	–.33	.75

Note. [1] mean results (standard deviations given in brackets); [2] number of persons (percentages given in brackets); * $p < .01$; ** $p < .05$; ° $p = .07$ the result on the level of statistical tendency.

LDL: Low-Density Lipoprotein;
HDL: High-Density Lipoprotein.

functions (intentional search, maintaining attention, attentional shift, graphomotor aspects of control, sequential information processing, and monitoring one's own behavior) we used the Color Trails Test for adults (CTT; r_{tt} .644–.787) Łojek, Stańczak, 2012). The Trail Making Test (TMT, parts A and B; Kądzielawa, 1990) from the Polish adaptation of the Halstead-Reitan Neuropsychological Battery was used to assess two abilities: whether an individual could maintain action orientation in his or her working memory, and how good one's executive control was. Finally, the ability to spontaneously produce words encoded and consolidated in the process of language acquisition was examined with the Controlled Oral Word Association Test (COWAT; Jodzio, 2008).

The main study, always carried out after the MRI scanning, was preceded by a case history and an in-depth assessment of laterality. The tests were administered in the following fixed order: CVLT (immediate recall of lists A and B, and short delay free recall of list A), TMT (parts A and B), CTT, COWAT, and CVLT (long delay free recall and long delay recognition). On average, the psychological examination took 50 minutes to complete.

Running fMRI scans

Functional magnetic resonance imaging (fMRI) of the brain was performed on a 3T Achieva TX (Philips Healthcare, Best, the Netherlands), using a 32-channel head coil. To analyze the fMRI data, we used a T2* Gradient Echo-Planar Imaging sequence (FFE-EPI: TR: 2000 ms, TE: 30 ms, Flip Angle: 90°, matrix: 64 x 64, slice thickness: 3 mm, 420 dynamic scans, voxel size: 3 x 3 x 3 mm, TA = 14 min, FOV = 250 mm).

The participants were asked to do a special version of the Stroop Color and Word Test (SCWT; Jodzio, 2008) in a rapid event design. This version of the test was adapted to be administered during fMRI scanning. To obtain the best possible contrast of the analysis-relevant tasks, the timings of individual stimuli were previously optimized using a genetic algorithm. Prior to the fMRI test, still outside the scanner tube, each participant had a training session to learn how to do the task. Inside the scanner, the test items were presented through special goggles adapted to work in a high magnetic field (NNL fMRI Visual System, Nordic Lab, Poland), and the participants' reactions were gathered through the response pads (NNL fMRI Visual System, Nordic Labs, Poland). Test items consisted of words or series of characters (control task). A participant had to decide what colors were shown – the task was to identify the colors of the font while ignoring the meaning of the words (incompatible color words) and to respond by pressing the right button. For the sake of later analysis, the results were categorized into four groups: Control (random strings of sings), Reading (the name of the color written in an unfilled black-outlined font), Compatible (the name of the color written in a font of a matching color), and Incompatible (the name of the color written in a font of an incongruent color). SCWT is expected to probe one's cognitive control over the distracting influence of automatic reading. To successfully complete the test, one has to be resistant to interferences and needs to demonstrate selective attention. Therefore, the method is used to measure one's executive control, i.e. one's inhibitory control in a situation when different pieces of information conflict (Lezak, Howieson, Loring, 2004; Jodzio, 2008; Jodzio, Biechowska, Szurowska, Gąsecki, 2011).

Statistical Parametric Mapping (version 12) implemented in MATLAB was used to analyze the data. We used standard procedures to prepare the data obtained from individual participants: the data were realigned to compensate for the motion artifacts (the first dynamic scan being the reference point), then spatially normalized (into the Montreal Neurological Institute template space; voxel size: 2 x 2 x 2 mm), and spatially smoothed with a Gaussian kernel of FWHM 6 mm. Once the data preparation phase was complete, we investigated the data with the Artifact Detection Toolbox to find any artifacts. We decided that a dynamic scan was affected by artifacts when a mean-volume signal varied from the preceding scan by more than three standard deviations, when motion rotation was greater than .02 degree, or when translation was greater than 1 mm. No participant obtained more than 10% of unreliable scans during the fMRI examination.

Next, a general linear model was developed using the prepared data. We estimated BOLD responses for four tasks given to the participants. The responses were modeled as rectangular functions with a duration of 2000 ms convolved with a standard hemodynamic function. Additional model regressors were the scans affected by artifacts and the motion coefficients (rotation and translation) obtained during the motion correction procedure. In order to remove low-frequency noise and scanner signal drift, the cleanup of the data was done with a high-pass filter with a cutoff frequency of 1/128 Hz.

Results

Results of neuropsychological examination

For the purpose of this paper the presentation of results was narrowed to ones relevant to the topic of the article, that is verbal and nonverbal executive control. The results of our analysis led us to believe that among HTN patients, as they were compared with the control group, only selective deficits in cognitive and executive functions exist. The criterion group members handled most of the tasks well and their scores were similar to those of healthy individuals. Differences between the groups could be observed only in some tests. Results that are important to the matter of this article are presented in Table 2.

Table 2. Mean scores obtained in selected tests (SD values given in brackets)

Method	Indeces	Criterion group n = 20	Control group n = 20	*P* (*t*-test[1]/U-Mann Whitney[2])
COWAT	Phonetic perseverations	.85 (1.2)	.15 (.4)	.001[1]
	Semantic perseverations	1.7 (1.8)	.75 (.9)	.05[1]
CVLT	Perseverations	5.4 (3.5)	2.25 (2.8)	.02[1]
	Intrusions	1.1 (1.6)	.8 (1.2)	n.s.[1]
Color Trail Test	CTT-1	37.9 (12.3)	33.5 (16.5)	n.s.[2]
	CTT-2	80.6 (29.1)	73.5 (25.1)	n.s.[2]
	CTT-1 NMNS	.75 (.9)	.2 (.4)	.05[2]
	CTT-2 NMNS	.4 (.6)	.2 (.4)	n.s.[2]
Trail Making Test	Part A	30.05 (9.9)	30.31 (11.3)	n.s.[2]
	Part B	83.9 (57.3)	63.8 (25.7)	n.s.[2]
	B/A ratio	2.67 (1)	2.19 (.7)	n.s.[2]

Note. **COWAT:** Controlled Oral Word Association Test;
CVLT: California Verbal Learning Test;
CTT: Color Trail Test scores;
CTT-1: completion time(in seconds) in the first part of Color Trail Test;
CTT-2: completion time (in seconds) in the second part of Color Trail Test;
CTT-1 NMNS: near-misses in number sequence in the first part of Color Trail Test;
CTT-2 NMNS: near-misses in number sequence in the second part of Color Trail Test.

Our attention was drawn to the perseverations rates in the Controlled Oral Word Association Test (COWAT). These rates are calculated both for the semantic and the phonetic aspect of COWAT. During the phonetic task ($t(12,1) = 1.68$; $p < .001$), perseverations were observed in 6 HTN patients (30%; $M = .85$; $SD = 1.2$) and only in 3 individuals from the control group (15%; $M = .15$; $SD = .4$). During the semantic task ($t(5,1) = 1.85$; $p < .05$), perseverations were observed in 13 HTN patients (65%; $M = 1.7$; $SD = 1.8$) and in 8 healthy individuals (40%; $M = .75$; $SD = .9$). Both types of perseverations, phonetic and semantic were observed in significantly fewer cases among healthy persons (55%) than among HTN patients (80%). HTN patients who manifested a tendency to perseverate, made this mistake habitually (as many as 3–8 times), often repeating a word or a series of words. Similarly, HTN patients produced more perseverations in CVLT ($M = 5.4$; $SD = 3.5$) than healthy individuals ($M = 2.25$; $SD = 2.8$): the mistakes were made by as many as 16 HTN patients (80%) compared to only 10 persons from the control group (50%). This disproportion suggests that HTN patients experience deficits in executive control, attention, and/or verbal memory.

The criterion group members, when compared with the control group, made more near-miss errors in the sequence of numbers in the first part of the Color Trail Test ($M = .75$; $SD = .9$; $p < .05$). The NMNS index describes how many situations there were when a participant initiated a wrong reaction (by attempting to connect a wrong pair of numbers), but corrected himself while drawing the line (eventually connecting the numbers correctly). The fact that the NMNS index takes on high values seems to confirm our earlier hypothesis that NTH patients potentially suffer from attention deficits and executive control disorders. They have difficulties performing simple tasks that do not require mobilizing much of their cognitive resources. More complex tasks, however, such as the second part of the Color Trail Test, pose no problems to them.

fMRI results – evaluating functional changes to the brain

In this article, the evaluation of asymmetrical cerebral activation was limited to the dorsolateral region of the prefrontal cortex. In the literature on the subject these regions, particularly the middle frontal gyrus, are considered neuroanatomical correlates of executive and control functions (Jodzio, 2008). To evaluate the asymmetrical brain responses we used task contrast (Congruent vs Incongruent), which emphasized the importance of inhibitory control. Calculations were performed with the LI-toolbox (Wilke, Lidzba, 2007). Then, using Student's *t*-test, we calculated group responses to contrasts of interests for every examined group. For the sake of comparative analysis, statistical maps showing brain activation were further limited to the middle frontal gyrus (area mask was generated using the WFU Pickatlas tool; Maldjian, Laurient, Kraft, Burdette, 2003). The significance level for the maps was set at $p < .01$ (with the FDR correction for multiple comparisons). The asymmetry index was calculated as the ratio of the difference of the number of active voxels in each hemisphere to the sum of active voxels in both hemispheres. In order to take activation at the voxel level into account, cluster analysis and variance weighting were performed when calculating the laterality index.

We found no important differences in SCWT scores obtained by different groups in the Control task ($t(22) = 1.34$; $p > .1$), Incongruous task ($t(35) = .57$; $p > .1$), and Reading task ($t(35) = -1.12$; $p > .1$). In the Congruous task, HTN patients scored higher than the control group, but the difference only reached the level of statistical "tendency" ($t(23) = -1.93$; $p = .07$). The results are presented in Table 3.

The fMRI laterality index (fMRI-LI) was calculated for the joint group effect of each group separately. This was done to account for the intra- and intersubject response variability. The individual single subject fMRI responses are prone to various distoring factors such as the signal session-to-session variability, personal BOLD response magnitude, differences in blood oxygenation, as well as differences in personal outcome. The averaged group responses on the other hand represent the intergroup difference between the brain areas involved in the contrast of interest (the inhibition control). Those maps served as basis for the fMRI-LI calculation.

If the fMRI laterality index value is between –.2 and .2, brain activation is considered symmetrical. Results

Table 3. Mean SCWT scores (*SD* values given in brackets)

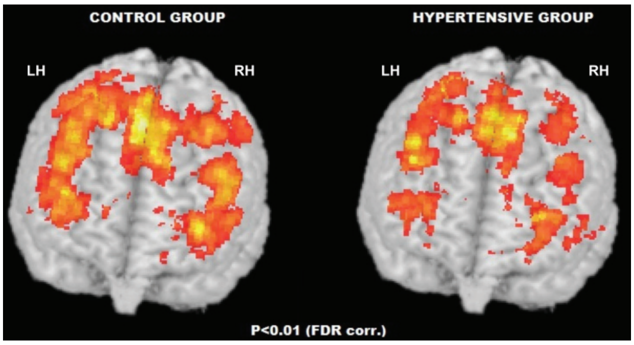
Method	Task	Criterion group n = 20	Control group n = 20	*t*-test	*p*
SCWT	Control	98.39 (1.53)	96.88 (4.64)	1.34	n.s.
	Congruent	98.54 (1.97)	96.05 (5.24)	1.93	.07°
	Incongruent	83.98 (30.29)	88.38 (13.35)	.57	n.s.
	Reading	96.07 (5.49)	93.61 (7.56)	1.12	n.s.
	Overall score	94.26 (7.87)	93.74 (7.35)	.20	n.s.

Note. ° $p = 0.07$ the result on the level of statistical tendency.

SCWT: Stroop Color and Word Test scores.

smaller than –.2 mean that there is a right asymmetry, and greater than .2 mean there is a left asymmetry. The fMRI-LI calculated for the dorsolateral prefrontal cortex (DLPFC) was .365 in the criterion group, which implies the left asymmetry. For the control group, the index was .02 which means the activity pattern was symmetrical. Figure 1 shows activation patterns for the groups.

Figure 1.



Finally, in order to examine the individual differences that underly the activation patterns in the groups, the percentages of correct responses during the fMRI task for each of the participants were further correlated with the results of the neuropsychological tests (the HTN and the CON group separately). The Spearman's correlation coefficient was used to control for a non-normality in the variables' distributions. As suggested by Brace et al. correlations ≥ ±.7 were considered as strong ones, ±.3–.6 – moderate, and ≤ ±.2 – weak (as cited in Mayers, 2013, p. 105). The values are given in the Table 4.

In the control group, the Incongruent SCWT score was found to correlate significantly with TMT-A (strong correlation) and with TMT-B (moderate correlation). Also, the Reading SCWT score correlated significantly (strong correlation) with TMT-B, CTT-1 and CTT-2. Among HTN patients, most of the calculated correlations of TMT-B with SCWT scores proved to be significant (strong or very strong correlations), except the correlation with the Congruent SCWT measure. This means that in patients with HTN there are strong negative relationships between TMT-B score and Control, Incongruent and Reading SCWT scores, and a very strong negative relationship between CTT-2 score and the Control SCWT score. High values of one variable correspond to low values of the other. In other words, HTN patients who needed less time (in seconds) to perform TMT-B and CTT-2 tasks were the same individuals who demonstrated the greater percentage of correct responses in some of the SCWT tasks (Control, Incongruent and Reading for TMT-B and Control for CTT-2).

Table 4. Relations between Trail Making Test and Color Trail Test times and the percentages of correct responses during the fMRI Stroop Color and Word Test for control and criterion group members (Spearman's *r* coefficient, *eta*^{2} effect size coefficient)

Method	Task		Criterion group (n = 20)				Control group (n = 20)			
			TMT A	TMT B	CTT-1	CTT-2	TMT A	TMT B	CTT-1	CTT-2
SCWT	Control	*r*	–.28	–.51	–.29	–.72	–.39	–.38	–.25	–.40
		eta^2		.23		.50				
		p		.028*		.001**				
	Congruent	*r*	.01	–.24	–.12	–.13	–.39	–.21	–.05	–.29
		eta^2								
	Incongruent	*r*	–.31	–.57	–.40	–.46	–.68	–.46	–.45	–.43
		eta^2		.77			.97	.92		
		p		.014*		.053°	.001**	.05*	.051°	.067°
	Reading	*r*	–.37	–.60	–.29	–.32	–.39	–.56	–.56	–.53
		eta^2		.76				.94	.72	.86
		p		.008**				.013*	.013*	.021*

Note. Correlation's significance is two-tailed: * $p < .05$; ** $p < .01$; ° $p = .07$ the result on the level of statistical tendency.

TMT: Trail Making Test scores;
TMT-A: completion time (in seconds) in the task A of the Trail Making Test;
TMT-B: completion time (in seconds) in the task B of the Trail Making Test;
CTT: Color Trails Test scores;
CTT-1: completion time (in seconds) in the first part of the Color Trails Test;
CTT-2: completion time (in seconds) in the second part of the Color Trails Test;
SCWT: Stroop Color and Word Test scores.

Finally, in order to examine the effect size in groups the *eta*^{2} coefficient was calculated. It explained the percentage of the total variance associated with each of the main effects. Accordingly to the brain activations (see: Figure 1) and to the *eta*^{2} coefficient results (see: Table 4) – the asymmetry of the HTN patients brain responses during the task execution in the MRI scanner is accompanied by a change of the correlation strength of the SCWT task scores (the correct responses), and TMT-B and CTT-2 scores (completion time). However in each of the groups – different profiles of correlations of the analyzed variables were found. Among HTN patients significant associations appeared between selected SCWT tasks, and TMT-B (with Incongruent and Reading SCWT tasks) and CTT-2 scores (with Control SCWT task). As for the Control group significant associations were found only between Incongruent and Reading SCWT tasks, and TMT-A, TMT-B, CTT-1 and CTT-2 scores.

Due to the convergence of cognitive processes involved in the execution of the tasks, the following discussion will be focused on correlation and the statistical power of the effect size for the Incongruent SCWT task, TMT and CTT scores.

Discussion

In our study, HTN patients produced more perseverations in verbal tests (COWAT, CVLT) and more near-misses (sequence of numbers CTT-1) than healthy individuals. This suggests that HTN patients experience deficits in executive control (especially in terms of verbal and graphomotor control), top-down attention, and verbal memory. HTN patients had difficulties in completing simple tasks that did not require them to mobilize greater cognitive resources. Moreover, a functional asymmetry in the inhibitory control processes was found during the fMRI task. Control group members demonstrated symmetrical brain responses, whereas the criterion group members demonstrated left-hemispheric dominance of brain activation during a task that required executive control. Also highlighted were strong and very strong negative relations between nonverbal measures of executive/control functions (TMT-B and CTT-2), the resistance to interference scores (Incongruent SCWT task) and the statistical power of the effect size in groups. The left-sided asymmetry for the middle frontal gyrus activation intensity among HTN patients favored weaker, compared to Controls, effect size between completion time of TMT-B and Incongruent and Reading SCWT tasks. The decrease in strength affects only the switching (TMT-B), but not the inhibition (CTT-2).

These findings can be best interpreted through the lens of structural and functional changes to the brain which occur in HTN. Structural changes probably refer to dysfunctional mechanisms of brain circulation, adverse effects of HTN on the CNS, or accelerated brain aging. It is possible that brains of HTN patients function differently (a different activity pattern in response to a cognitive stimulus is observed) as a result of mechanisms aimed to compensate the condition's negative effects. It is well known that HTN impairs the functioning of the CNS and accelerates brain aging (Jennings et al., 2008). Consequently, the structure, functions, and organization of the brain's blood vessels are changed (Farkas, Luiten, 2001). As a result, resting cerebral blood flow is reduced and we can observe dysfunctions of the mechanism responsible for brain circulation (op. cit.). Cerebrovascular diseases play an essential role in reducing one's cognitive capabilities and can affect one's behavior as well. Most often, behavioral consequences include either executive deficits resulting from one's inability to maintain one's attention and from impaired cognitive processes, or a generalized, nonspecific deterioration of one's cognitive functioning. HTN-related cognitive deficit supports the hypothesized relation between cerebrovascular diseases and one's attention or executive functions (Li et al., 2015).

It is therefore possible that the difficulties experienced by HTN patients were (as mentioned by Farkas and Luiten, 2001) a consequence of cerebrovascular changes, especially those belonging to the spectrum of small vessel diseases or cerebral microbleeds (CMB; Nyenhuis, 2014). The etiology and cognitive consequences of CMB, similarly to those of cerebrovascular dementia, depend on the lesion's location. Cognitive deficits probably result from indirect structural damage to tissue surrounding a microbleed, its dysfunction, impaired reactivity of the brain's small vessels, or disrupted neurotransmission between frontal lobes and subcortical structures (Werring et al., 2010). Most often, neuropsychological problems include a generalized, nonspecific cognitive deterioration (microbleeds located in the temporoparietal and subcortical regions) and executive dysfunctions (microbleeds in the basal nuclei and frontal lobes). Memory functions, speech, and thinking processes are rarely affected (Seo et al., 2007; Werring et al., 2010).

HTN's patients uninhibited cognitive responses and the left-hemispheric dominance of brain activation may be a consequence of functional changes to the brain – ones that are not detected during a fMRI examination. This hypothesis is in keeping with the theory by Jennings et al. (2008) – these authors claimed that HTN patients experience holistic changes to the brain understood as an integrated system. This assumption gained additional support when the researchers from John Hopkins University in Baltimore asked HTN patients to perform a Flanker Task inside an fMRI scanner. The patients, compared with the control group, did poorer on the task, and the researchers attributed that to increased activation of the left parietal lobe. The Flanker Task (cf. Eriksen, Eriksen, 1974; Nęcka, Orzechowski, Szymura, 2006) is used to assess one's ability to suppress responses to non-target stimuli (called flankers). The method is often considered to be equivalent to the Stroop test. Chuang (*op. cit.*) found that HTN patients are more susceptible to distraction, which would explain why disinhibition symptoms develop.

For our discussion, the fMRI findings that confirm the left-hemisphere dominance in asymmetry of information-processing are of special diagnostic importance. Differences between our own findings and the results obtained in 2014 by Chuang et al. (frontal lobes vs parietal lobes) most probably result from using different cognitive tasks in the MRI scanner (SCWT vs the Flanker Task). It is significant, however, that the results obtained with the magnetic resonance correspond to the results of the neuropsychological examination. The asymmetry of inhibitory processes (which are needed for correct executive control) is reflected in poor performance in neuropsychological tests. Verbal perseverations, both in COWAT and in CVLT, point to verbal inhibition disorders. On the other hand, a high value of the CTT's near-miss index implies delayed nonverbal inhibition (in this case: graphomotor inhibition). Furthermore, the analysis of the effect sizes (see: Table 4) leads to the conclusion that the occurrence of asymmetric cerebral response during the execution of a task requiring inhibition control in a conflict situation (Incongruent SCWT task) makes it difficult to predict the results of tasks evaluating executive control outside of the MRI scanner.

Disorders in suppressing verbal and motor reactions were diagnosed in patients with a history of cerebral stroke (Jodzio et al., 2011). In those studies, patients were asked to perform conflicting motor reactions (the go/no-go task) and to complete the SCWT test. A significant majority of the participants failed to complete at least one of the tasks. In our study, however, more than 90% of patients demonstrated deficits in control, especially in its verbal (numerous perseverations in verbal tests) and graphomotor aspect. On the other hand, all participants did well on the Stroop Color and Word Test. The only differences were found in the fMRI scanner and revealed that different brain regions were activated. SCWT checks everyday activities such as reading and color recognition. Going against the automatic responses (verbal perseverations) or impulsive graphomotor actions (CTT's near-miss errors) requires mental discipline and learning new ways of reacting. Difficulties observed in HTN patients are probably a consequence of a process going on in the CNS and similar to that observed in the study by Jodzio et al. (*op.cit.*). Control disorders, as a manifestation of the more broadly defined executive dysfunctions are difficult to find in persons with no general cognitive disorders – even using mental state screening tests, during routine medical examinations, or with nonfunctional neuroimaging. This mechanism manifests itself in a functional rather than structural way, and its character is more selective than general. Considering that long-term effects of HTN on one's vascular system increase the likelihood of (among others) brain stroke (Bobrie et al., 2008), it appears safe to assume that the results are an early warning signal of the changes to come. In other words, both kinds of inhibition disorders are a sign of progressing executive disorders. As the condition advances, these disorders may become more pronounced. In the initial stages of HTN, however, they can be detected with a set of selected neuropsychological tests.

The cognitive impairments we observed among HTN patients prove the condition's detrimental effect on one's CNS. Effective executive control, inhibition included, requires both of the brain's hemispheres to work together – as evidenced by the fMRI results showing left asymmetry in HTN patients (cf. Figure 1), high values of inhibition indexes obtained in neuropsychological tests (cf. Table 2), and correlation coefficients and effect size (cf. Table 4).

For further examinations, we plan to include more patients with the following conditions in the criterion group: arterial hypertension, resistant arterial hypertension, transient ischemic attack, and obstructive sleep apnea. We plan to include individuals with normal and high-normal blood pressure in the control group. A larger sample of examined persons will allow us to perform more in-depth statistical analyses, which in turn will reinforce the result's diagnostic and clinical validity.

Limitations

The primary challenge of this project is a relatively small group of participants which limits possible interpretations and analyses. Therefore the fMRI-LI was calculated for the joint group effect and not for specific subjects individually, since considering the group size – the individual fMRI-LI measures will characterize a very large variance. The use of four different neuropsychological test suggests the necessity of a correction for multiple comparisons. Unfortunately, due to limited size of the group, the use of correction would likely produce false negatives (i.e. reducing statistical power). Therefore for subsequent research it is highly recommended to use this type of correction and the individual fMRI-LI measures on a bigger population of patients.

Conclusions

1. Around 90% of HTN patients were found to demonstrate selective disorders of executive control (especially verbal and graphomotor control).
2. When completing tasks that required significant self-control, HTN patients typically demonstrated left-hemispheric dominance of brain activation, as measured by fMRI. Manifestations of disinhibition were further supported by a detailed neuropsychological examination.
3. Both the cognitive (measured with the tests' results) and neurophysiological characteristics of the examined persons indicate that both cerebral hemispheres actively participate in controlling the execution of selected cognitive tasks.
4. The cognitive impairments we found among HTN patients prove the condition's detrimental effect on one's CNS.

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Appendix 1

Shapiro-Wilk test results of Trail Making Test, Color Trail Test times and the fMRI Stroop Color and Word Test for control and criterion group members

Method	Task	Criterion group (n = 20)		Control group (n = 20)	
		Shapiro-Wilk Test	*p*	Shapiro-Wilk Test	*p*
SCWT	Control	.83	.005	.71	.001
	Congruent	.75	.001	.72	.001
	Incongruent	.52	.001	.80	.01
	Reading	.61	.001	.74	.001
CTT	CTT-1	.95	.43	.77	.001
	CTT-2	.76	.001	.76	.001
	Near-miss error CTT-1	.71	.001	.51	.001
	Near-miss error CTT-2	.70	.001	.51	.001
TMT	TMT-A	.89	.03	.63	.001
	TMT-B	.72	.001	.62	.001