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SIGNIFICANTLY LOWER RIGHT MIDDLE CEREBRAL ARTERY BLOOD FLOW VELOCITY IN THE FIRST EPISODE OF PSYCHOSIS DURING NEUROCOGNITIVE TESTING

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SUMMARY

Background: *Changes in cerebral hemodynamics have been reported in schizophrenia and proposed as underlying the cognitive deficits seen in patients. The objective of our study was to compare changes of the cerebral blood flow velocity (BFV) during neurocognitive tasks between the patients with the first episode of psychosis and healthy controls.*

Subjects and methods: *We recruited 46 patients with the first episode of psychosis (FEP), admitted to the University Hospital Centre Zagreb during 2016-2017 and 41 control subjects. Transcranial Doppler ultrasonography monitoring of BFV in both middle cerebral arteries was recorded during 25-minute long neurocognitive assessment with Phonemic Verbal Fluency test, Trial Making Test B and Stroop test. Between every consecutive test resting periods were recorded.*

Results: *After the adjustment for age, sex and education by quantile regression, patients with FEP had significantly lower BFV in middle cerebral arteries during the 3rd (Δ-15, Δ%-28% p=0.023) and 4th task (Δ-15, Δ%-28% p=0.031) of the Stroop test and the 1st task of Foot tapping test (Δ -16, Δ% -30% p=0.034). We observed significantly lower changes of right middle cerebral artery BFV in FEP between two consecutive tests in all four tasks of the Phonemic verbal fluency test, 1st and 2nd task of the Stroop test and Trail making test, and the1st task of Foot tapping test; and of the left artery between first three tasks of the Phonemic verbal fluency test, the last one of the Phonemic verbal fluency test and all first three tasks of the Stroop test.*

Conclusions: *Decreased middle BFV during the execution of particular neurocognitive tasks in patients with FEP, compared to control subjects might indicate impaired hemodynamic function in the prefrontal/parietal brain areas, and possibly provide an explanation of some of the observed neurocognitive deficits in patients with the first episode of psychosis.*

Key words: *intracranial blood flow - first psychotic episode - neurocognitive test – neuroimaging - schizophrenia*

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INTRODUCTION

Schizophrenia is one of the most disabling psychiatric illnesses, affecting about 1% of population worldwide (Nishanth et al. 2017). In majority of cases, schizophrenia is a chronic illness with a recurrent course, characterized by alternating periods of acute psychotic illness and their remission (Clementz et al. 2016, Hallmayer et al. 2005). The first episode of psychosis (FEP) usually follows a prodromal period of unspecific affective and cognitive symptoms and functional decline, and is characterized by a cluster of positive (e.g. delusions, hallucinations), negative (e.g. abulia, anhedonia), cognitive (e.g. impaired attention or abstract reasoning, executive functioning), affective (e.g. depression) and psychomotor symptoms (e.g. agitation). With each new episode of acute psychosis, the patient condition deteriorates further, until a stage with predominately negative and cognitive symptoms is reached, contributing to an overall decrease of patients functioning (Andreasen et al. 2005). Thus, neurocognitive deterioration is present from the beginning of the illness (Mesholam-Gately et al. 2009) and significantly influence the course of the illness (On et al. 2016, Rund et al. 2016).

Huge efforts have been made to identify a biological correlate of schizophrenia in order to objectify the diagnosis and course of illness, yet without straightforward results (Kim et al. 2010, Lai et al. 2016, Weickert et al. 2013).

One stream of investigation used neuroimaging methods that have shown possible structural and functional deficits in brains of patients with schizophrenia (Pantelis et al. 2005, Honey and Bullmore 2002). Some of these results were interpreted as results of cerebral hemodynamics in patients with schizophrenia and also with first episode psychosis, although results are inconsistent (Santra & Kumar 2014, Kanahara et al. 2013, Tsujino et al. 2011, Wake et al. 2010, Molina et al. 2005, Riehemann et al. 2001, Hoptman & Antonius 2011). As well as with other techniques, many studies that included Transcranial Doppler (TCD) ultrasonography

to measure cerebral blood flow velocity (BFV) and pulsatility in main intracranial arteries with excellent temporal resolution (Wintermark et al. 2005), indicated that patients suffering from schizophrenia or even FEP have different intracranial hemodynamics compared to the healthy population (Owega et al. 1998, Lee et al. 2008, Lee et al. 1999), but the results are overall inconsistent.

Since studies using TCD have shown that cognitive activation have effect on BFV in a healthy population (Boban et al. 2014a, Boban et al. 2014b, Stroobant & Vingerhoets 2000, Vingerhoets & Stroobant 1999, Schuepbach et al. 2012, Connaughton et al. 2017, Frauenfleder et al. 2004) researches explored effect of neurocognitive activation on a BFV in patents with schizophrenia (Schuepbach et al. 2002, Feldmann et al. 2006, Schuepbach et al. 2016, Schuepbach et al. 2017, Sabri et al. 2003) and found significant effect of neurocognitive activation on BFV, but in different directions. Heterogeneity of results can partially be explained with heterogeneous sample, different illness phase, possible effect of chronic use of antipsychotic medication etc.

None of these studies had a sample of patients with FEP. That is why we conducted a study on a sample of patients with FEP and healthy controls. The aim of our study was to compare changes of BFV in both MCAs, recorded by TCD, while patients and controls were exposed to activating neurocognitive paradigm consisting of three consecutive neurocognitive tasks (Phonemic verbal fluency test, Trial making test B and Stroop test).

SUBJECT AND METHODS

Subjects

The sample consisted of 46 patients with FEP and 41 control subjects. We chose a consecutive sample of patients by the order of their admission to the hospital at the Department of Psychiatry, University Hospital Centre Zagreb in the period from January 2016 to December 2017. A convenient sample of healthy volunteers was chosen among hospital staff and medical students as the control group. Inclusion criteria were: patients ≥ 18 years old, diagnosed with the first episode of psychosis (FEP) following the criteria of International Classification of Disorders, 10th revision (ICD-10 codes F23, F29) (WHO 2007). The diagnosis was made by two experienced psychiatrists separately. In the case of disagreement, the final decision was to be reached by a consensus (in all cases the experts diagnoses were identical). Exclusion criteria were mental illness in childhood that can present with psychosis (such as autism), organic psychosis, neurological disorders, mental retardation, comorbid alcoholism or use of opiates, pregnancy and lactation, the use of medications that can produce psychotic reactions.

Procedures

This cross-sectional study was conducted as a part of prospective cohort study, as stated in the Acknowledgements section.

Written informed consent was obtained from the participants and the study was approved by the Ethical committee of University Hospital Centre Zagreb.

The study was done in accordance with World Medical Association Declaration of Helsinki 2013.

All 46 patients were recruited by experienced psychiatrists up to the third week of treatment. Upon study inclusion, all subjects were interviewed by the study researchers. General information was obtained from each subject (age, medical history, education) using a structured questionnaire, constructed for the purpose of the study. Clinical assessment included Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), and were performed by two experienced raters. Consensus based rating was agreed upon, so in the case of disagreement, the final score was discussed and agreed upon between raters. Interrater reliability was high (Cohen's kappa, κ=0.84).

Additionally, handedness was determined by using Edinburgh Handedness Inventory (EHI) (Oldfield 1971).

Experimental paradigm

Blood pressure (BP), heart rate (HR) and visual analog anxiety scale (VAS) were assessed before and after computer paradigm was performed by a study researcher. Prior to testing all cognitive tasks were verbally explained to subjects. Also precise instructions of what exactly is expected from subjects were displayed on the screen prior to each task. (For example: For the next task you are going to use paper and a pen. On the paper you will see numbers from 1 to 13 and letters from A to L. During the 45 seconds you are supposed to draw a line, alternating in order between the numbers and letters. Start at number 1 then go to the first letter, A, then go to the next number, 2 and then the next letter, B and so on.) During performance of cognitive tasks (presented on a computer screen), TCD monitoring of BFVs in both middle cerebral arteries (MCAs), as well as HR were recorded. Subjects were sitting in a semi-dark, quiet room looking at a computer screen showing the ongoing computer paradigm.

The paradigm consisted of three cognitive tasks lasting approximately 25 minutes. The paradigm was chosen based on the literature search and based the previous work of the research group who showed that these tests elicited BFV changes in the left and right MCAs in healthy population (Boban et al. 2014a). The initial phase included the resting period in which the subject was sitting relaxed, watching the computer screen for 180 seconds (s). This phase was followed by breath-holding (BHI) test which lasted for up to 30 s with a subsequent 120 s resting period in which the subjects were required to breathe normally. A two-minute resting period took place between each task. The preliminary

testing showed that this period of time is sufficient for BFV and HR to return to basal levels. During the resting periods the participants were sitting relaxed and looking at a conventional screen saver on the computer screen (Starfield, Microsoft Corp., USA). Neurocognitive paradigm consisted of 1) Phonemic verbal fluency test (pVFT) designed to assess verbal ability and verbal executive functioning (Szirmai et al. 2005). Participants were instructed to pronounce silently as many words as they could recollect in 25 s beginning with the given letter (with the exception of proper names). Since they were supposed to pronounce it silently we did not record pronounced words. Five seconds later they were asked to say out loud the number of generated words and the number was written in the form designated for the purpose of this research. This task contained four subtasks with 4 different letters (K, F, N, S); 2) Stroop test with incongruent stimuli requires executive functions: during this cognitive task a list of color names was displayed on the screen with a mismatch of color name and color ink; the subjects were required to ignore the displayed color name and to name the color ink over 25 s, paying close attention to precision and rapidity (Golden 1976). This task also contained four subtasks; 3) Trial Making Test B (TMT B) which activates executive functions. This cognitive task was presented on a piece of paper and it was made of numbers (1–13) and letters (A-L) (Tombaugh 2004). The goal was to connect numbers and letters alternately in ascending order in a 45-s time limit (1-A-2-B-3-C-. . .-13). After performing the three tasks described patients were asked to carry out the Foot tapping test to check lateralization which lasted 30 seconds for each leg. All phases during the neurocognitive testing are shown in Table 1.

TCD monitoring

The monitoring was done with the 2 MHz pulse-wave TCD device (Doppler-BoxX, DWL) probes placed bilaterally over trans temporalwindow at a 55-60 mm insonation depth which is related to M1 segments of MCAs (Aaslid et al. 1982, Von Reutern et al. 2000). The probes were placed by a experienced study researcher. The probes were held in a place by the head frame. Time resolution of the device was 0.01 s.

Mean values were calculated automatically by the system using equation: MBFV (Vsis + 2Vdis)/3; (MBFV = mean blood flow velocity, Vsis = peak systolic velocity, Vdis = peak diastolic velocity). Averaging of MBFV values was done for sequential 5-s time intervals for each subtask separately reaching a final mean value for each task and each subject. Averaging of 5 s intervals was done with 0.5 s of overlapping between intervals (28). Distance between Vsis peaks was used to calculate the heart rate which was averaged using the same 5-s intervals (Szirmai et al. 2005). Considering significant difference in actual values of MBFV among participants we used relative MBFVs (MBFVrel) that were calculated by the following equation: MBFVrel = (MBFVact/ MBFVref) x 100; MBFV act being the actual MBFV during the observed interval and MBFV ref being the MBFV velocity during the -15 to -3 prestimulus period of the resting interval (Knecht et al. 1988, 2000).

Table 1. Duration of neurocognitive testing phases

Phase ID	Slides	Duration (sec)	Description
1	1-5	170	Initial inaction
2	6-9	14	Preparation for BHI
3	10-39	30	BHI
4	40-41	120	Rest after the BHI
5	42-45	28	Description of task 1.
6	46-48	5	Preparation for the task 1.1.
7	49-50	25	Task 1.1.
8	51-53	5	Result 1.1.
9	54-55	60	Rest after the task 1.1.
10	56-58	5	Preparation for the task 1.2.
11	59-60	25	Task 1.2.
12	61-63	5	Result 1.2.
13	64-65	60	Rest after the task 1.2.
14	66-68	5	Preparation for the task 1.3.
15	69-70	25	Task 1.3.
16	71-73	5	Result 1.3.
17	74-75	60	Rest after the task 1.3.
18	76-78	5	Preparation for the task 1.4.
19	79-80	25	Task 1.4.
20	81-83	5	Result 1.4.
21	84-85	120	Rest after the task 1.4.
22	86-88	24	Description of the task 2.
23	89-90	2	Preparation for the task 2.1.
24	91	25	Task 2.1.
25	92-94	60	Rest after the task 2.1.
26	95-96	2	Preparation for the task 2.2.
27	97	25	Task 2.2.
28	98-100	60	Rest after the task 2.2.
29	101-102	2	Preparation for the task 2.3.
30	103	25	Task 2.3.
31	104-106	60	Rest after the task 2.3.
32	107-108	2	Preparation for the task 2.4.
33	109	25	Task 2.4.
34	110-112	60	Rest after the task 2.4.
35	113-116	19	Description of the task 3.
36	117	45	Task 3.
37	118-120	120	Rest after the task 3.
38	121-122	2	The announcement of the task 4.
39	123-125	17	Preparation for the task 4.1.
40	126	30	Task 4.1.
41	127-129	60	Rest after the task 4.1.
42	130-132	17	Preparation for the task 4.2.
43	133	30	Task 4.2.
44	134-135	6	Rest after the task 4.2.

BHI - Breath holding test; Task 1 - Phonemic verbal fluency test (pVFT); Task 1.1, 1.2, 1.3, 1.4 - subtasks of Phonemic verbal fluency test; Task 2 - Stroop test with incongruent stimuli; Task 2.1, 2.2, 2.3, 2.4 - subtasks of Stroop test; Task 3 - Trial making test B; Task 4 - Foot tapping test; Task 4.1, 4.2 - subtasks of Foot tapping test

Statistical analysis

The main analysis was performed by the quantile regression. Median intracranial blood flow velocities were adjusted for age, sex and education. Two study groups were different in regard to self-perceived stress measured by visual-analogue scale. FEP patients reported higher baseline stress score then healthy controls (median (interquartile range) 29 (9-51); 20 (3-35) respectively) (Table 2). We did not controlled the effect of this variable as it is possible that it has causal effect on the intracranial blood flow.

Originally, BFV was measured by TCD in millseconds, and were transformed to seconds before the analysis. Statistical significances were not corrected for multiple testing because all analysis was pre-planned. The level of statistical significance was set at a two-tailed $p<0.05$, and all confidence intervals (CI) were at the 95% level. Statistical data analysis was done by NCSS 10 Statistical Software (2015) (NCSS, LLC. Kaysville, Utah, USA).

Table 2. Participants baseline sociodemographic and clinical characteristics

	First psychotic episode (n=46)		Healthy control (n=41)	
Gender, n (%)				
male	25	(54.3)	14	(34.1)
female	21	(45.7)	28	(66.7)
Age (years)	26	(21-34)	30	(25-34)
Years of education	12	(12-16)	18	(16-18)
Dominant hand (right), n(%)	43	(93.5)	38	(95.0)
Arterial blood pressure (mmHg)				
systolic	120	(110-125)	117	(110-124)
diastolic	80	(70-81)	77	(63-80)
Elevated arterial blood pressure (systolic>130 ordiastolic>80 mmHg), n (%)	11	(23.9)	11	(27.5)
Heart rate (bpm)	80	(73-99)	77	(70-83)
EHI augmented index	87	(67-100)	87	(68-100)
Self-perceived stress (VAS scale)	29	(9-51)	20	(3-35)
PANSS total score	107	(88-118)		
Specific PANSS symptoms scales				
positive	26	(22-32)		
negative	26	(22-30)		
general	54	(47-58)		

Data are presented as median (interquartile range) if not stated otherwise

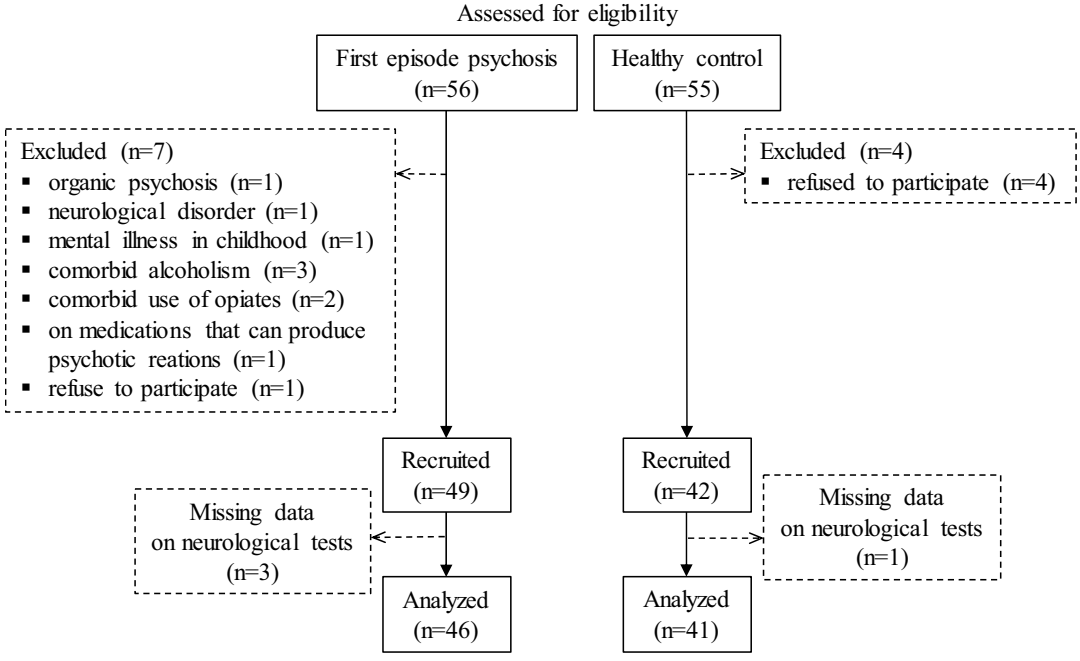


Figure 1. Participants flow

RESULTS

We assessed 56 FPE patients and 55 healthy healthcare professionals for the eligibility (Figure 1). Finally, we analyzed the data on 46 FEP patients and 41 healthy control group participants. Two groups were markedly different regarding gender, age, education, and self-perceived stress (Table 2). Our two study groups were comparable with regard to dominant hand, EHI augmented index, arterial BP and HR. After the adjustment for age, sex and education by quantile regression, we have not observed significant differences between the two study groups regarding the MBFV in the left and right MCAs in resting state. However, FEP patients had significantly lower MBFV in the right MCA during the 3rd and 4th task of the Stroop test and the 1st task of Foot tapping test (Table 3).

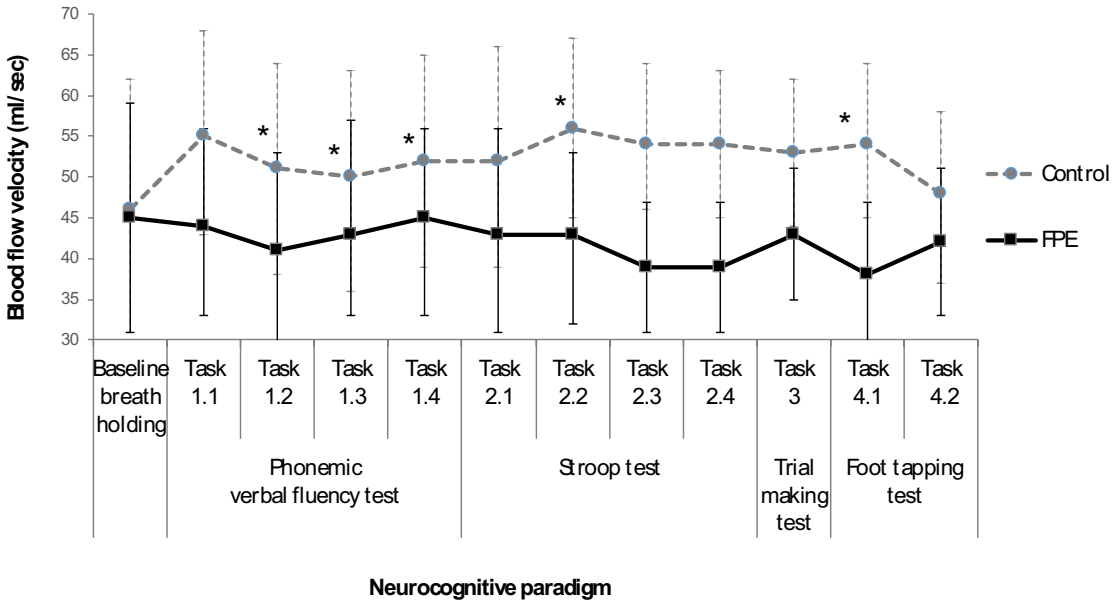
Significant differences between FEP and healthy control group in changes of the right MCA blood flow velocity between two consecutive neurocognitive tests were observed between all four tasks of the Phonemic verbal fluency test (Δ-2.7, Δ% -142%, p 0.033, Δ-3.3, Δ% 1-22%, p 0.001, Δ-1.8, Δ%-90% , p 0.044) between 1st and 2nd task of the Stroop test (Δ-2.6, Δ% -79%, p 0.045) and between the Trail making test and the1st task of Foot tapping test (Δ-2.4, Δ%-69%, p 0.038). In all these cases the change was lower in FEP than in healthy control group, as shown in Figure 2.

In the left MCA significant differences between FEP and control group in the changes of blood flow were observed between 1st,and 2nd (Δ%-2.4, Δ%-109%, p 0.036) and2nd and 3rd task of the Phonemic verbal fluency test (Δ-4.3, Δ%-108%, p 0.006), between the last one of the Phonemic verbal fluency test and the 1st task of the Strop test (Δ-4.6, Δ%-71%, p 0.036) and between all of the first three tasks of the Stroop test (Δ-3, Δ%-77%, p 0.025, Δ-5.5, Δ%-131%, p 0.008). In all these cases the change was lower in FEP than in healthy control group as shown in Figure 3.

Table 3. Middle cerebral artery (MCA) median blood flow velocity adjusted for age, sex, and education

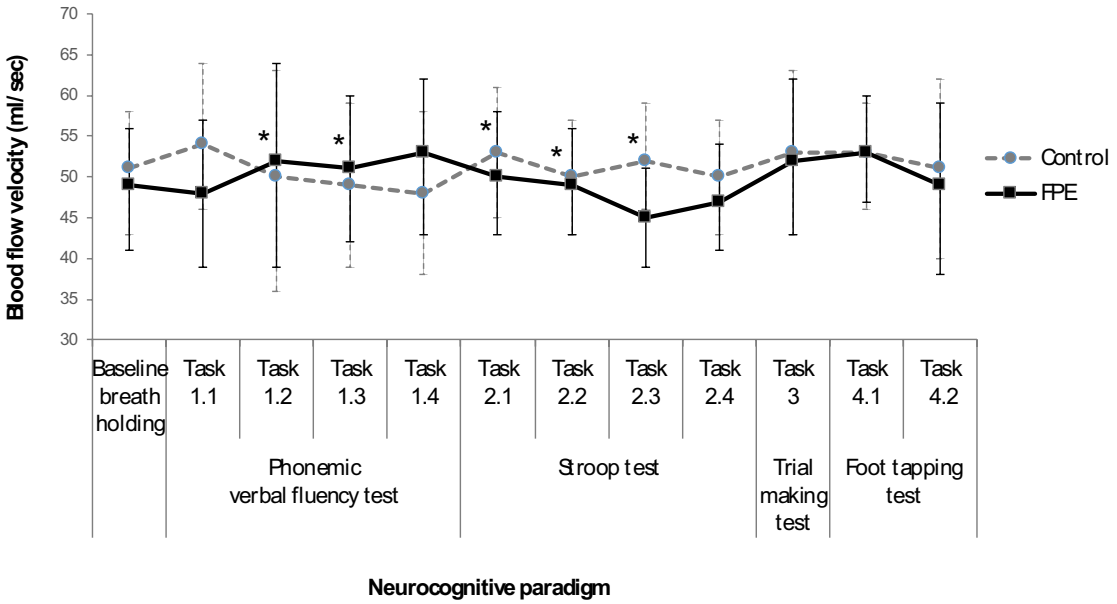
	First psychotic episode (n=46)		Healthy control (n=41)		Δ	Δ%	p
Right							
Baseline during breath hold	45	(31-59)	46	(31-62)	-1	-2%	0.918
Phonemic verbal fluency test							
Task 1	44	(33-56)	55	(43-68)	-11	-20%	0.279
Task 2	41	(29-53)	51	(38-64)	-10	-20%	0.345
Task 3	45	(33-57)	50	(36-63)	-7	-14%	0.661
Task 4	45	(33-56)	52	(39-65)	-7	-13%	0.449
Stroop test							
Task 1	43	(31-56)	52	(39-66)	-9	-17%	0.394
Task 2	43	(32-53)	56	(45-67)	-13	-23%	0.129
Task 3	39	(31-47)	54	(46-64)	-15	-28%	0.023
Task 4	39	(31-47)	54	(45-63)	-15	-28%	0.031
Trial making test	43	(35-51)	53	(44-62)	-10	-19%	0.163
Foot tapping test							
Task 1	38	(28-47)	54	(45-64)	-16	-30%	0.034
Task 2	42	(33-51)	48	(37-58)	-6	-13%	0.472
Left							
Baseline during breath hold	49	(41-56)	51	(43-58)	-2	-4%	0.740
Phonemic verbal fluency test							
Task 1	48	(39-57)	54	(46-64)	-6	-11%	0.353
Task 2	52	(39-64)	50	(36-63)	2	4%	0.869
Task 3	51	(42-60)	49	(39-59)	2	4%	0.815
Task 4	53	(43-62)	48	(38-58)	5	10%	0.576
Stroop test							
Task 1	50	(43-58)	53	(45-61)	-3	-6%	0.730
Task 2	49	(43-56)	50	(43-57)	-1	-2%	0.880
Task 3	45	(39-51)	52	(46-59)	-7	-13%	0.184
Task 4	47	(41-54)	50	(43-57)	-3	-6%	0.610
Trial making test	52	(43-62)	53	(43-63)	-1	-2%	0.911
Foot tapping test							
Task 1	53	(47-60)	53	(46-59)	0	0%	0.882
Task 2	49	(38-59)	51	(40-62)	-2	-4%	0.747

Data are presented as median (95% confidence interval) adjusted for age, sex, and education
Abbreviations: Δ = absolute difference between adjusted medians in FEP and control group; Δ% = difference between adjusted median in FEP and control group relative to the adjusted median in control group; p = statistical significance of the difference calculated by quantile regression



Abbreviations: Δ = absolute difference between adjusted median change in FEP and control group; Δ% = difference between adjusted median change in FEP and control group relative to the adjusted median of change in control group; p = statistical significance of the difference calculated by quantile regression

Figure 2. Right middle cerebral artery (MCA) median intracranial arteries blood flow velocity during all neurocognitive tests adjusted for age, sex and education; error bars represent 95% confidence intervals



Abbreviations: Δ = absolute difference between adjusted median change in FEP and control group; Δ% = difference between adjusted median change in FEP and control group relative to the adjusted median of change in control group; p = statistical significance of the difference calculated by quantile regression

Figure 3. Left middle cerebral artery (MCA) median intracranial arteries blood flow velocity during all neurocognitive tests adjusted for age, sex and education; error bars represent 95% confidence intervals

DISCUSSION

We have compared changes in BFV in MCAs during cognitive test performance in 46 patients with FEP compared to a 41 healthy controls. As to our knowledge, this is the largest study using TCD which involved patients with FEP. First, we found that patients with FEP had significantly lower MBFV in the right MCA during the Stroop neurocognitive test of executive functioning. In addition we found smaller changes in MBFV between two consecutive neurocognitive tasks in both MCAs in patients compared to control, indicating that the differences in BFV during the active task and resting state was significantly larger in control subjects compared to patients with FEP.

In few studies described in the literature, where TCD was performed without activation paradigms, authors found increased BFV in a sample of 28 and 20 patients with FEP compared to healthy subjects (Owega et al. 1998, Lee et al. 2008), or found no differences in BFV in a sample of 55 patients with schizophrenia and 15 patients with FEP in comparison to healthy controls (Lee et al. 1999).

In studies that used TCD to detect specific BFV during neurocognitive tasks (Schuepbach et al. 2017, Schuepbach et al. 2016, Feldmann et al. 2006, Schuepbach et al. 2002a, Boban et al. 2014a, Schuepbach et al. 2002b, Boban et al. 2014b) variable results have been obtained. Our results are compatible with the studies of Feldmann et al. (2006) and Schuepbach et al. (2002a) where authors found decreased BFV in both MCAs using TCD during Stockings of Cambridge (SOC) and Winsconsin Card Sorting Test (WCST) and task Tower of Hanoi (TOH) in patients with schizophrenia compared to controls. Interestingly the same group of authors compared BFV during SOC in patients suffering from schizophrenia with and without extrapyramidal symptoms and found that the group with EPS have blunted BFV during difficult mental planning task of SOC suggesting that EPS in schizophrenia have detrimental effect on BFV (Schuepbach et al. 2017). All mentioned tests test executive functions. TOH test measures executive functions with non-verbal content and requires spatial perception of position (Welsh et al. 1991). WCST is a classic neuropsychological test that measures prefrontal dysfunctions in adults (Welsh et al. 1991) and SOC is a part of Cambridge Neuropsychological Test Automated Battery (CANTAB) designed to measure planning efficacy (Ozonoff et al. 2004).

However, contrary to our result, Schuepbach et al. (2016) found that BFV is increased in patients with schizophrenia during TMT B activation test. Thus, some of the explanation of these differences may be the challenging potential of specific tests, as was observed with studies using PET (Shulman et al. 1997). For example in a sample of healthy population Boban et al. (2014a) used pVFT, Stroop test and TMT and found that TMT B test is associated with the greatest blood flow increase in MCAs. Also in a sample of healthy population Scuepbach et al. (2002b) compared hemodynamic response to activation tasks TOH and WCST and found that TOH showed an increased mean BFV in MCAs as compared with the WCST during the steady state. Interestingly, the same authors found increased BFV in both MCAs in patients with schizophrenia using TMT B as an activating task (Schuepbach et al. 2016), but found decreased BFV in when using TOH (Schuepbach et al. 2002a) in another sample of patients with schizophrenia.

The MCA supplies lateral part of prefrontal lobe, lateroinferior part of the frontal lobe, lateral part of parietal lobe, temporal lobe and basal ganglia (Tatu et al. 2012). Thus, alterations of hemodynamics would possibly affect language expression and verbal understanding, visuospatial functions and working memory. Conversely, tasks that activate these functions may require increase of BFV in MCA (Boban et al. 2014a). Taking into consideration that neuronal coupling describes a close temporal and regional linkage between neuronal activity and cerebral blood flow responses (Phillips 2016) our finding could be in agreement with findings from functional imaging studies in schizophrenia that showed altered activation of prefrontal cortical areas during tasks of executive function, working memory or planning compared to controls (Taylor et al. 1996, John et al. 2011, Fujiki et al. 2013, Henseler et al. 2009).

However there are studies suggesting major role of brain microcirculation in schizophrenia and occurrence of microvascular abnormalities in brains of patients suffering from schizophrenia (Prabakaran et al. 2004, Hanson & Gottesman 2005, Harris et al. 2008). Subtle alterations of microvessel could lead to compromised brain metabolism and oxidative stress potentially causing disruptive neuronal coupling (Hanson & Gottesman 2005). However other studies found no alteration in microvessel length questioning the hypothesis of alterations in microvasculature in schizophrenia (Kreczmanski et al. 2009). It is still unclear whether possible changes in the brain circulation may effect neuronal coupling and subsequently neurocognitive or other symptoms, as well as what is the degree of possible disruption that is necessary for the impairment to produce neurocognitive symptoms."

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Decrease of the BFV in these areas may also support the findings of the loss of structural connectivity in FEP (Skudlarski et al. 2010).

The fact that differences in BFV between patients and control were found only in the right MCA during active performance of the Stroop test may reflect different aspect of processing possibly activated by the test, in example, visuopatial information processing, which is under dominance of the right hemisphere (Woolley et al. 2010). Indeed, studies found lateralization differences in BFV in right hemisphere using TCD compared with the

left during neurocognitive challenge with heterogeneous results, that seems to depend upon experimental factors, task demands or other processes inherent to the task (Vingerhoets & Stroobant 1999, Bulla-Hellwig et al. 1996). For example some authors did not find any differences between hemispheres during performance of two visuospatial tasks that required mental rotation of complex figures (Hartje et al. 1994) while others found that difficult mental planning provoked lateralization to the right hemisphere (Schuepbach et al. 2012). Interestingly, Feldmann et al. (2006) found that female patients with schizophrenia had subtly higher BFV in the right MCA than male patients especially during solving difficult problems indicating possible gender-related differences.

Although there is considerable heterogeneity across studies and especially methods used, neurocognitive functions in schizophrenia are commonly divided into following domains: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, social cognition (Corigliano et al. 2014, McCleery et al. 2014). Meta-analysis done by MesholanGately et al. (2009) additionally divided attention domain into 3 subdomains: processing speed, working memory and vigilance. According to the literature, cognitive impairment in a patient with schizophrenia and FEP are present in all cognitive domains (Corigliano et al. 2014, Gold et al. 2004); but more prominent in specific domains such as verbal memory, processing speed and verbal fluency (MesholanGately et al. 2009, Henry et al. 2005) and these domains are specifically activated by the tests that we included in this study.

Another finding of this study were the observed statistically significant differences in changes of BFV between two consecutive neurocognitive tests in both arteries. In the state between two consecutive tasks, the subjects were in the resting state. In all cases the changes were smaller in the FEP group compared to healthy subjects, indicating that the differences in BFV during the activating task and resting state were significantly larger in control subjects compared to patients with FEP. We can assume that in the resting state hemodynamic may be impaired in both MCAs in patients with FEP. This result is compatible with the concept of an altered default mode network (DMN). Concept of an altered DMN was suggested by Raichle et al. (2001) who found that the differences in activation between patients and controls exist in patients during the resting state. We can assume lower brain's intrinsic functionality when it is at "rest" in patients and failing to deactivate during the initiation of a tasks. It is hypothesized that patients with schizophrenia show inability to suppress the default mode network in response to tasks. The biological correlate of the default mode network alteration is the loss of anatomical connections in the regions including the posterior cingulate cortex and adjacent precuneus (pCC/PCUN), medial prefrontal cortex (mPFC), mesial and inferior temporal lobes (mTL/iTL), and inferior parietal lobe, and formation of functional (but not anatomical) hyperconnectivity as a compensation mechanism, which in turn produces a state of hyprealertness (Hu et al. 2017). It is questionable whether decreased capability to change BFV in response to activating tasks reflects or contributes to a possible structural hypoconectivity of the regions supplied by the MCAs. Another possible explanation may be the specific response of the FEP group to internal stimuli. It is questionable whether patients with FEP may be more anxious compared to controls during the "resting state", possibly producing a state of distress, and consequently elicit a state of sympathetic activation. Interestingly, Lee et al. (1999) reported statistically significantly smaller oscillations of a pulsatible index of the BFV using TCD in patients with schizophrenia and FEP compared to a healthy subjects in both MCAs, suggesting that vessel's 'adjustment ability' in distal resistance of patients with FEP is diminished. He argues that cerebral autoregulation, as the physiological regulatory mechanism that maintains constant brain blood flow over wide ranges of arterial blood pressure is impaired in patients with schizophrenia even in FEP possibly due to different mechanisms such as the interplay of sympathetic and vagal stimulation of humoral factors affecting blood vessels (Lee et al. 1999). According to MacKenzie et al. (1997) sympathetic activation, associated with a drop in perfusion pressure, will cause constriction of the large resistance vessels and dilatation of smaller resistance vessels farther downstream as an autoregulatory response. Thus, state of high sympathetic activation, such as observed in the state of emotional distress (Goldstein 2013) in persons with impaired cerebral autoregulation may possibly explain less ability to increase BFV in response to activating tasks, such as found in control subjects.

This study contributes to identification of possible markers that may objectify the diagnosis of psychosis, and possibly objectify the progression of illness/ treatment. To further investigate the potential of identified changes, as to serve as biomarkers of the progression of illness/ treatment, we shall perform a follow up study of these patients for 18 months and assess changes of BFV in correlation with cognitive status in the phase of remission. Furthermore, it could possibly contribute to the identification of biological (hemodynamic) changes underlying neurocognitive deficits seen in patients with FEP while performing neurocognitive tasks. This could-contribute to better understanding of a possible alteration of patterns of hemodynamic activation underlying neurocognitive processing in the first episode psychosis.

This study has several limitations. First, as we chose a consecutive sample of patients with FEP and the convenient sample from the healthy control population the study has the increased risk of the sample bias and lower probability of representativeness for the targeted populations. Second, our healthy control group was chosen from the population of healthcare professionals.

It is quite likely that this population is less affected by the white-coat hypertension effect than the population with FEP. If it is so, it is reasonable to expect that the BP lowers more in FEP than in the control group during the initial inaction which lasted for two minutes. If the BP is associated with the cerebral blood flow, this might induce the bias. Third, our sample may not be treated as the representative for the entire Croatian population of patients with FEP, although there is no ground for the assumption that cerebral blood flow is systematically different in different regions of the country. Fourth, although all subjects in our study were young, and treated only up to three weeks with antipsychotics, we cannot exclude the effects of medication on BFV. Fifth, we did not adjusted our results for the baseline stress because it may be the mediator of FEP association with intracranial blood flow.

CONCLUSIONS

In conclusion we have compared changes in BFV in both MCAs, during cognitive test performance in 46 patients with FEP compared to a 41 healthy controls. As to our best knowledge, this is the largest study using TCD involving patients with FEP.

We found that patients with FEP had significantly lower BFV in the right MCA during neurocognitive test of executive functioning. In addition we found smaller changes in BFV between two consecutive neurocognitive tasks in both MCAs in patients compared to controls. Our results support the hypothesis of altered cerebral hemodynamics even in the first episode of schizophrenia, which are evident under activation. This study also emphasizes a potential of TCD use in exploring BFV in patients with FEP while under cognitive activation.

Contribution of individual authors:

Ivana Kekin: conception and design of the study; acquisition and analysis of data; drafting the manuscript and tables; writing the final version of the manuscript:

Dina Bosnjak: conception and design of the study, acquisition of data; drafting and writing the final version of the manuscript;

Porin Makaric: conception and design of the study, drafting the manuscript and tables;

Zarko Bajic: data analysis, drafting the manuscript and table, writing the final version of the manuscript;

Linda Rossini Gajsak: conception and design of the study, drafting the manuscript and tables;

Branko Malojcic: conception and design of the study, analysis of data; drafting the manuscript and tables;

Marina Boban conception and design of the study, drafting the manuscript;

Martina Rojnic Kuzman: conception and design of the study, analysis of data; drafting the manuscript and tables; writing the final version of the manuscript.

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