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Gender differences in cognitive functions: retrospective analysis of the data of 5 neuropsychological studies

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Abbreviations: NS, not significant; WAIS, Wechsler Adult Intelligence Scale; DAT, Delayed Alternation Test; WCST, Wisconsin Card Sorting Test; TMT A ,TRAIL MAKING TEST part A; TMT B ,TRAIL MAKING TEST part B; WMS, Wechsler Memory Scale; POCD, postoperative cognitive dysfunction; IQ, intelligence quotient

ABSTRACT

The gender differences in verbal and visuospatial cognitive domains and mathematics are well known and documented in psychometric research. Nevertheless, the findings in this field are consistent predominantly for academic but not for neuropsychological studies. Here we present the results of the retrospective analysis of the data of our five neuropsychological studies, conducted in cardiologic and psychiatric patient cohorts. We intended to analyze the consistency of gender effects in similar patient populations and to determine the possible co-factors, which may increase or diminish the intergroup differences in cognition in males and females. In all five studies we used the core battery of tests (Digit Span, Digit Symbol and Block Design) in the variable combination with other tests, sensitive to global mental status, intelligence, memory and leaning, verbal fluency, psychomotor speed, executive functions The most consistent pattern of gender differences with the advantage of females in verbal fluency and psychomotor speed tests and the advantage of males in the visuospatial reconstruction test was observed in the youngest psychiatric patient cohort (mean age – 31 years). Our data are consistent with the previous findings of prominent hormonal effects on the performance on verbal fluency, visual rotation and motor speed. Nevertheless, the partial gender effects on cognitive functioning with the advantage of females on Digit Symbol or the advantage of males on Block Design were observed in older cardiologic patient populations as well. The inconsistency of gender effects on the cognitive performance in older patient populations may be the consequence of the concomitant effects of aging and pathological processes on brain functioning, which may confound the gender effects. Overall, these findings support the recommendation to analyze the neuropsychological data of females and males separately, especially when using tests with high sensitivity to gender effects in young and hormone-replacement therapy patient populations.

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1. Introduction

Gender distribution in patient cohorts is an important factor, which may influence results of the investigation of neuropsychiatric disorders. The data of neuroanatomical and neurofunctional studies consistently demonstrated, that brain is organized and functioning somewhat differently in females and males. At the same time, the data of neuropsychological studies in this field are more variable and inconclusive.

Males in all age groups are characterized by the approximately 8 – 15% larger mean brain volume in comparison with females, and respectively by larger absolute volumes of almost all neuronal and conductive brain structures. [1, 2] Overall, the male brain is structurally more asymmetrical than the average female brain. [3, 4] In the context of cognitive functioning, the most important findings concern gender differences in the organization of visual and auditory cortical regions. These are characterized by larger relative volumes of primary and secondary visual cortex in males and by larger relative volumes of primary auditory and left temporal cortex in females [5-7]. Interestingly, meta-analysis of 25 neuroanatomical studies showed, that female cohorts demonstrated higher correlations between brain structure volumes and the verbal intelligence, and, in contrast, males are characterized by higher correlations between the brain neuroanatomy and non-verbal cognitive functions. [3, 8, 9]

The neurophysiology is different in females and males as well, with the higher amplitude of brain electric activity in female cohorts in comparison with males. The latter finding was reported for both spontaneous [10, 11] and evoked brain electric activity [12, 13]. This may indicate that females tend to generalize brain electric activity with the simultaneous involvement into the information processing of more neurons in comparison with males, while the latter are characterized by the more localized and probably stepwise information processing. In accordance with the results of neuroanatomical studies, in the neurophysiologic study by Neubauer and colleagues [14] the females demonstrated larger correlations between the intelligence quotient (IQ) and the electric activity at the left hemisphere derivations, and in contrast the males showed the same correlations to be larger for the right hemisphere. Interestingly, in the study by Williams and colleagues [15] the correlation between the oddball-task related gamma-activity synchrony and the gray matter volume was positive for females and negative for males. These data evidence that the cognitive activity is supported by the electric neural activity in different spectral band frequencies in females and males, and this is in agreement with the data of our study of gender effects on the resting-state brain electric activity [11]. The latter showed that default-mode networks oscillations were characterized by different mean frequencies in females and males.

The gender differences in verbal and visuospatial cognitive domains and mathematics are well known and documented in psychometric research. Nevertheless, the findings in this field are consistent predominantly for academic but not for neuropsychological studies. For instance, the meta-analysis of 1.5 million's children reading achievements showed that girls outperformed boys in all 75 nations ($0.36 < d < 0.65$) [16]. Whereas, Wai and colleagues [17] analyzed the male-female mathematical ability ratios from over 1.6 million 7^{th} grade students across 30 years and found the stable advantage of males in mathematical reasoning especially in the highly complex mathematical tasks. Interestingly, that gender differences in academic verbal and mathematical skills diminished in the last decades, but still were detectable [17, 18]. At the same time, the summarized cognitive indexes as the verbal or non-verbal intelligence quotients or g-factors are commonly equal in females and males [3, 19, 20].

Male advantages in mental rotation tasks were demonstrated among all age groups including 3 months infants [18, 21]. Nevertheless, the gender effects on other visuospatial tasks are less consistent. For instance, in the study by Lakin & Gambrell [20], which included approximately 150 000 school students, the figural subtest with paper folding favored boys, whereas the figure classification subtest favored girls in almost all age groups. This means that 'non-verbal' character of the test does not automatically give the advantage to male participants of the investigation.

Here we present the results of the retrospective analysis of the data of our five neuropsychological studies, conducted in cardiologic and psychiatric patient cohorts. We intended to analyze the consistency of gender effects in similar patient populations and to determine the possible co-factors, which may increase or diminish the intergroup differences in cognition in males and females.

2 Methods

2.1 Subjects

The detailed description of our patient cohorts and control subjects are presented elsewhere. The Studies 1, 2, and 3 were conducted in the Bakulev's cardiovascular surgery center since 2002 to 2012 and were aimed to investigate intraoperative and electroencephalographic correlates of postoperative cognitive dysfunction (POCD) in cardiac surgery patients. The study design was explained to the patients, and each patient gave an informed consent to participate. Subjects were excluded if they had a history of stroke or other neurologic or psychiatric disease; if they were undergoing reoperative surgical procedures; if they were unable to perform the cognitive test battery due to visual problems or non-Russian-speaking. Inclusion criteria were: age 16 - 69 years old and cardiac ejection fraction > 40%. Here we present only preoperative testing results.

The Study 1 (Table 1) was purposed to determine the effects of the intraoperative cerebral microembolic load on the postoperative cognitive functioning [22, 23]. The objective of the Study 2 (Table 2) was the investigation of perioperative brain electric activity [23, 24]. Here we excluded from the analysis the patients with ischemic heart disease due to cerebrovascular disease in some of them. Thus, only younger patients with mitral/aortic valve disease and matched controls from the Studies 1 and 2 are presented here. Due to small female sample in the Study 3 (Table 3), which was aimed to determine the sensitivity of a range of neuropsychological tests to POCD [23], all patients and control subjects are presented here.

Table 1. Demographic and neuropsychological differences in male and female cohorts of cardiologic patients and controls in the Study 1.

	Males N=25	Females N=23	Intergroup differences
Age, years	48.6 ± 13.3	46.5 ± 13.0	NS
Education, years	13.9 ± 2.6	13.4 ± 2.3	NS
Mini-Mental State Examination	27.0 ± 2.2	26.1 ± 2.4	NS
WAIS Information subtest	23.7 ± 3.8	24.1 ± 3.2	NS
WAIS Digit Span Forward	6.32 ± 1.07	5.74 ± 1.10	NS
WAIS Digit Span Backward	4.76 ± 0.83	4.35 ± 1.11	NS
Logical memory test	11.8 ± 2.3	11.1 ± 2.8	NS
Luria memory test	8.10 ± 0.98	8.17 ± 1.10	NS
WAIS Digit Symbol	42.8 ± 11.9	40.0 ± 7.78	NS
WAIS Block Designs	**38.3 ± 6.7**	**32.5 ± 7.8**	**t=2.77, p=0.008**
Benton Visual Retention Test	7.24 ± 1.83	7.04 ± 1.26	NS
Trail Making Test, part A, time	50.2 ± 8.4	53.8 ± 9.6	NS
Trail Making Test, part B, time	78.0 ± 18.6	84.9 ± 19.5	NS

Values are expressed as mean ± SD.
Abbreviations: NS, not significant; WAIS, Wechsler Adult Intelligence Scale.

Table 2. Demographic and neuropsychological differences in male and female cohorts of cardiologic patients and controls in the Study 2.

	Males N=18	Females N=31	Intergroup differences
Age, years	45.5 ± 12.0	42.3 ± 13.9	NS
Education, years	14.6 ± 3.0	14.6 ± 2.7	NS
Mini-Mental State Examination	28.2 ± 2.0	27.7 ± 2.7	NS
WAIS Digit Span Forward	6.17 ± 1.34	6.52 ± 1.09	NS
WAIS Digit Span Backward	4.78 ± 1.44	5.35 ± 1.52	NS
WAIS Digit Symbol	**42.7 ± 12.4**	**54.3 ± 12.2**	**t=3.21, p=0.002**
WAIS Block Designs	38.8 ± 8.3	39.9 ± 8.2	NS

Values are expressed as mean ± SD.
Abbreviations: NS, not significant; WAIS, Wechsler Adult Intelligence Scale.

Table 3. Demographic and neuropsychological differences in male and female cohorts of cardiologic patients and controls in the Study 3.

	Males N=32	Females N=13	Intergroup differences
Age, years	49.2 ± 13.4	49.0 ± 13.8	NS
Education, years	14.3 ± 2.9	13.7 ± 2.3	NS
WAIS Information subtest	23.2 ± 5.6	24.5 ± 0.7	NS
WAIS Vocabulary subtest	60.5 ± 12.1	63.2 ± 9.3	NS
WAIS Digit Span Forward	6.35 ± 1.26	6.13 ± 1.08	NS
WAIS Digit Span Backward	4.77 ± 1.07	4.63 ± 1.21	NS
Category Verbal Fluency	39.7 ± 11.0	38.5 ± 10.0	NS
WAIS Digit Symbol	40.6 ± 11.3	40.5 ± 10.6	NS
WAIS Block Designs	35.8 ± 10.1	34.2 ± 5.3	NS
Tower London Test	7.97 ± 2.39	6.92 ± 1.51	NS
	N=24	N=9	
WAIS Comprehension subtest	21.2 ± 2.9	22.3 ± 2.5	NS
WCST, perseverative errors	6.17 ± 7.40	8.44± 9.21	NS
WCST, non-perseverative errors	3.78 ± 4.16	4.67 ± 2.92	NS
DAT, perseverative errors	**13.3 ± 6.9**	**8.2 ± 4.1**	**t=2.61, p=0.015**
DAT, non-perseverative errors	24.9 ± 5.9	21.9 ± 6.1	NS
	N=7	N=7	
Stroop Test, time	74.3 ± 27.0	69.2 ± 25.9	NS
Pegboard test dominant, number of pegs	15.6 ± 1.6	17.1 ± 2.7	NS
Pegboard test non-dominant, number of pegs	14.0 ± 2.8	16.3 ± 2.4	NS

Values are expressed as mean ± SD.
Abbreviations: DAT, Delayed Alternation Test; NS, not significant; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

The fourth study (Table 4) was conducted in the Scientific Practical Psychoneurological Center and was purposed to test a non-verbal tool for screening diagnostics of depression and anxiety in neurotic patients [25]. The majority of in-patients needed psychiatric treatment due to stressful life events.

Inclusion criteria were:

(1) age 18 – 70 years old;

(2) education length ≥ 10 years.

Exclusion criteria were:

(1) psychotic symptoms;

(2) a history of stroke or other serious neurological disease;

(3) deficits of vision or hearing. The study design was explained to subjects, and each subject gave a written informed consent.

Table 4. Demographic and neuropsychological differences in male and female cohorts of psychiatric patients and controls in the Study 4.

	Males N=24	Females N=55	Intergroup differences
Age, years	33.3 ± 12.8	34.4 ± 12.3	NS
Education, years	15.2 ± 2.7	14.4 ± 1.5	NS
WAIS Vocabulary subtest	48.5 ± 12.5	48.1 ± 14.8	NS
WAIS Digit Span Forward	6.38 ± 1.10	6.18 ± 1.22	NS
WAIS Digit Span Backward	4.71 ± 0.75	4.82 ± 1.06	NS
WAIS Digit Symbol	47.0 ± 12.7	46.7 ± 11.8	NS
WAIS Block Designs	39.0 ± 7.4	37.6 ± 8.9	NS
Luria memory test	7.38 ± 1.04	7.33 ± 1.38	NS

Values are expressed as mean ± SD, where appropriate.
Abbreviations: NS, not significant; WAIS, Wechsler Adult Intelligence Scale.

The fifth study (Tables 5) is ongoing, and its aim is to determine the sensitivity of neuropsychological tests to cognitive dysfunction in patients with primary affective disorder complicated by short-term alcohol abuse. The inclusion and exclusion criteria are similar to the fourth study. Each subject gave a written informed consent to participate in the study.

Table 5. Demographic and neuropsychological differences in male and female cohorts of psychiatric patients and controls in the Study 5.

	Males N=14	Females N=23	Intergroup differences
Age, years	30.4 ± 8.4	31.3 ± 7.9	NS
WAIS Vocabulary subtest	65.1 ± 9.1	62.6 ± 8.3	NS
WAIS Digit Span Forward	6.93 ± 1.54	6.70 ± 1.23	NS
WAIS Digit Span Backward	5.50 ± 1.40	5.52 ± 1.23	NS
Category Verbal Fluency	41.6 ± 9.2	48.2 ± 5.7	t=2.67, p=0.011
WAIS Digit Symbol	44.9± 9.0	53.0 ± 8.1	t=2.82, p=0.008
WAIS Block Designs	44.3 ± 1.9	36.9 ± 10.3	t=2.49, p=0.027
Benton Visual Retention Test	7.93 ± 1.54	7.78 ± 1.38	NS
Tower London Test	9.50 ± 1.02	9.13 ± 2.26	NS
WCST, perseverative errors	4.86 ± 3.80	3.43 ± 3.98	NS
WCST, non-perseverative errors	6.71 ± 5.36	2.83 ± 3.24	t=2.76, p=0.009

Values are expressed as mean ± SD.
Abbreviations: NS, not significant; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

2.2 Neuropsychological assessment

The cardiologic patients completed neuropsychological tests in 2-3 days prior to surgery, the psychiatric patients were tested during the first 3 days after hospitalization. In all five studies we used the core battery of tests (Digit Span, Digit Symbol and Block Design) in the variable combination with other neuropsychological tests. Overall, we used 18 neuropsychological tests. The following cognitive domains were assessed:

2.2.1 Global cognitive status:

MINI MENTAL STATE EXAMINATION (MMSE) [26], included 30 simple questions and tasks in a number of areas: orientation in time and place, repeating and recalling list of words, arithmetic (the serial sevens), language use and comprehension, non-verbal memory - the summarized score was analyzed.

2.2.2 Verbal intelligence:

The INFORMATION subtest of Wechsler Adult Intelligence Scale (WAIS) [27] required subjects to answer standard questions concerning general knowledge. The COMPREHENSION subtest of WAIS consists of a set of questions concerning everyday situations or proverb interpretation. VOCABULARY subtest of WAIS implies subjects giving precise definitions to a standard set of words ranging in frequency of usage in everyday language. The raw scores were included into the analysis.

2.2.3 Verbal short-term memory and verbal learning:

DIGIT SPAN FORWARD of WAIS [27] required subjects to repeat a series of digits that have been orally presented to them in forward order; DIGIT SPAN BACKWARD OF WAIS required to repeat a series of digits in reverse order; LOGICAL MEMORY TEST of Wechsler Memory Scale (WMS) required subjects to repeat as many semantic items in the short story as possible; LURIA MEMORY TEST included learning of 10 words during 5 trials. For the former three tests - the maximal span of the repeated items, and for the Luria test - the mean number of words during 5 trials were included into the analysis.

2.2.4 Verbal fluency:

First subjects were asked to generate as many names from the semantic category 'animals' within 60 seconds as possible [28]. Then they were instructed to repeat this task with the category 'fruits'. Sum of generated words was included into the analysis.

2.2.5 Visuospatial construction:

The BLOCK DESIGN test of WAIS [27] involved subjects to reconstruct the geometric designs using either four or nine, two-tone colored blocks; the raw score of the test was analyzed.

2.2.6 Visual memory:

BENTON VISUAL RETENTION TEST [28]: the subjects were asked to reproduce from memory 10 designs after 10 seconds exposure, one at a time, as exact as possible; the number of exact completed designs were included into the analysis.

2.2.7 Motor speed:

The PEGBOARD TEST requires the subject to place cylindrical pegs into the board with holes as quickly as possible with the score being the number of pins placed in 30 seconds.

2.2.8 Psychomotor speed:

DIGIT SYMBOL of WAIS [27] involved subjects to code, within 90 seconds, as many digits into symbols as possible - raw score was analyzed; TRAIL MAKING TEST part A (TMT A): the subjects were asked to connect 25 numbers consecutively, as quickly as possible - the time taken to complete the test was analyzed.

2.2.9 Planning:

TOWER OF LONDON TEST [29] consisted of 12 look-ahead puzzles in which three differently colored rings had to be moved from a starting configuration on three sticks to a target position in a minimum number of moves. The number of problems solved at the first attempt in less than 60 seconds was scored.

2.2.10 Cognitive flexibility:

WISCONSIN CARD SORTING TEST [30]: Three stimulus dimensions (color, form and number) were represented on stimulus cards, and subjects were required to sort the cards, according to each of the dimensions. After the subject determined the correct rule for the match and made a series of correct responses, the rule was changed without warning and the subject again had to determine the new correct rule. Protocols were scored for number of perseverative errors within the context of 128 card administration.

2.2.11 Reward loading test:

DELAYED ALTERNATION TEST [31]: The subjects were not told that the correct answer alternates on every trial from being on the same to being on the opposite side as the previous one. Every next trial the one rouble coin was put into one of two reinforcement wells not chosen on the preceding trial. The learning criterion was 12 consecutive correct responses. Failure criterion was 50 trials. Errors were scored.

2.2.12 Interference:

The effects of interference on cognitive performance we investigated with two tests. The TRAIL MAKING TEST part B (TMT B) [28] required subjects to connect numbers and letters in sequential and alternative order (1, A, 2, B, etc.) - the time of the performance was analyzed; the STROOP TEST first required subjects to read two ‘congruous’ lists of color names and after that to name incongruous colors of the ink, in which were printed inconsistent color-words (for instance the word “red” is printed in green ink). In our study participants made few errors, therefore the time of the completion of the third part of the test is presented.

2.2.12 Statistics

For statistical analysis SPSS software for windows (SPSS 17.0, Chicago, IL, USA) was used. Intergroup differences were evaluated by Student’s t-tests.

3 Results

3.1 Global cognitive status

There were no gender differences in MMSE in two our studies, which included this test.

3.2 Verbal functions

3.2.1 Verbal intelligence

There were no gender differences in verbal intelligence tests in four studies, which included Information and/or Vocabulary and/or Comprehension subtests of WAIS.

3.2.2 Verbal short-term memory and verbal learning

In all five of our studies were used Digit Span forward and Digit Span backward subtests, and neither of the former showed gender differences in the performance on these tests. Verbal learning was as well not influenced by gender in two our studies, which included Luria memory and Logical memory tests.

3.2.3 Verbal fluency

We used Category Verbal Fluency test in two studies, and one of them (Table 5) showed significant advantage of females in this test in comparison with the male group. Interestingly, that psychiatric patients in this study were almost 20 years younger in comparison with the cardiologic patients. The mean age of females and males in the psychiatric study was 30 – 31 years.

3.3 Visuospatial functions

3.3.1 Visuospatial construction

We used the Block Design subtest of WAIS in each of our five studies, and in two of them (Table 1 and 5) we found gender differences in the expected direction, i.e. males outperformed the females. The intergroup differences were considerable, in average the male groups showed 6 – 8 points larger results in comparison with the female groups. In two other studies males also showed better results, but the intergroup differences did not reach significance. In the other study the somewhat younger female group showed insignificantly better results in comparison with the males.

3.3.2Visual memory

We used Benton Visual Retention Test in two studies. Although the males showed somewhat better results, the intergroup differences did not reach significance.

3.4 Motor and psychomotor speed

3.4.1 Motor speed

We used the Pegboard test only in one study with a small number of patients. The males tended to perform on this test faster, but the intergroup differences were not significant.

3.4.2 Psychomotor speed

We used the Digit Symbol subtest of WAIS in all 5 studies, and in two of them (Table 2 and 5) we observed gender differences in the predicted direction, i.e. the females outperformed the males. In addition, we used the TMT, part A in one study, which did not demonstrate the gender effect on psychomotor speed neither on TMT A, nor on the Digit Symbol.

3.5 Executive functions

3.5.1 Planning

We used the Tower of London test in two studies, and did not found significant gender differences in the performance on this test.

3.5.2 Cognitive flexibility

We used Wisconsin Card Sorting Test in two studies and we found no gender differences in the number of perseverative responses in either of them. Nevertheless, in one of these studies (Table 5) with somewhat younger patients, the males showed significantly more non-perseverative errors in comparison with the female subgroup.

3.5.3 Reward loading test

In the Delayed Alternation Test, which we used only in one cardiologic study (Table 3), the males demonstrated significantly more perseverative responses in comparison with the female subgroup.

3.5.4 Interference

We used the Stroop test and the TMT B test in two different studies and observed no gender effects on the performance on tests with the interference in neither of them.

4 Discussion

In the present study we evaluated 12 cognitive domains, and in 6 of them the significant gender effects were determined. Overall, the registered gender effects were in the expected direction, however were not consistently confirmed in all studies, which used the similar tests. The most pronounced gender differences in cognitive functioning we found in the relatively young, small and homogenous population of patients with affective disorder and alcohol abuse. In the larger population of patients with affective disorder of somewhat older age the gender effects on cognitive functioning were not at all registered.

4.1 Verbal fluency

The advantage of females in verbal fluency tasks was demonstrated in a range of studies and in average is equal to 0.33 standard deviation (d). At the same time the gender differences in vocabulary tests are commonly negligible (0.02 d) [21], what is similar to our findings. Interestingly, in the study of Weiss and colleagues [32], male students outperformed females in the vocabulary test, whereas female students showed significantly better results in the verbal fluency and the verbal learning. The neuroimaging study by Bell and colleagues [33] demonstrated the significantly greater mean activation of the prefrontal, parietal and cingulate cortex during the word generation task in the male cohort in comparison with the female one, and this fact may indicate the greater demand of word generation to cognitive resources in male subjects in comparison with more automatic responses during the task in females.

We evaluated only category (semantic) verbal fluency, which was significantly better performed by the young females with affective disorder in comparison with the matched males. The 20 years older cardiologic cohort did not demonstrate intergroup differences. Some data indicated that the verbal fluency was increased in females in the midluteal in comparison with the follicular phase and correlated positively with the estradiol level [34]. Hence, the discrepancy of the gender effects on the performance on the verbal fluency test in two our studies may be probably explained by the differences in hormonal status between the postmenopausal females in the cardiologic cohort and the females of reproductive age in the psychiatric cohort. It should be noted, that very few postmenopausal females in Russia received hormone-replacement therapy in the period of our cardiologic studies.

4.2 Visuospatial construction

We used the Block Design test in all five of our neuropsychological studies, but only two of them demonstrated the gender effects in the expected direction, i.e. the advantage of the male cohort in comparison with the females. Again the youngest psychiatric patient population showed the intergroup differences. The same was characteristic for the cardiologic cohort, which did not include patients with atherosclerosis.

The Block Design subtest of WAIS loads highly on the spatial and mental rotation processing, and therefore our findings of the gender differences in the performance on this test are logical. Nevertheless, the gender effects on the Block Design were not frequently reported, and we could identify only one study, which investigated the former. Waber and colleagues [35] found significant differences between girls and boys aged 6 – 18 years in this test favoring boys, which were not associated with any gender effects on the Matrix Reasoning, Spatial Working Memory or Spatial Span tests. These findings are similar to ours, as we also did not find gender differences in the performance on Benton Visual Retention Test or Tower of London Test, which loading on visuospatial processing but with minimal involvement of mental rotation in comparison with the Block Design test.

Previous studies showed that males outperformed females in mental rotation tasks with an average effect size of 0.56 standard deviation [21]. However, some data indicated that the male advantage in mental rotation was characteristic only for right-handed subjects [36], and probably may be influenced by high/low masculinity traits [37] and hormonal status [21]. Interestingly, in the study by Maki and colleagues [34] females performed the mental rotation task significantly better early in the follicular phase (low hormones) in comparison with the midluteal phase, and the performance on this cognitive test negatively correlated with the estradiol serum concentration.

4.3 Psychomotor speed

Two of our studies demonstrated gender effects on the performance on the classical psychomotor speed test, *i.e.* Digit Symbol subtest of WAIS. Again, the prominent intergroup difference in this test was shown by the youngest cohort of psychiatric patients. In addition, the gender differences in Digit Symbol were registered in the youngest cardiologic patient cohort. Both female groups in these studies outperformed all other male and female groups in our database and showed the equal to each other results. The advantage of females in Digit Symbol and Coding tests was also demonstrated in the study of children aged 6 – 18 years by Waber and colleagues [35].

Females commonly show higher motor and psychomotor speed in relatively simple tests [32, 35, 38, 39]. However, the psychomotor speed in tests highly loading on visual processing was reported to be higher in males [39]. In the present study we also used the Pegboard test, which is a classical motor dexterity task and was also shown to be performed significantly faster by young female cohorts in comparison with male ones [35]. Our middle-aged female group of cardiologic patients also tended to perform this motor dexterity task faster in comparison with the males, however, due to small number of participants intergroup difference did not reach significance.

The absence of the gender effects in three other studies may be explained by the contribution of other co-factors, strongly influencing the performance on Digit Symbol and other psychomotor/motor speed tests. First, the Digit Symbol test is highly sensitive to aging and concomitant pathological processes in brain [40, 41]. For instance, in the study by Swan and colleagues [40] the performance on the Digit Symbol test declined in average by 4 points at the reassessment in 5 years in a cohort of 50 – 60 years old males. The magnitude of the decline was the largest in older and less educated subjects with the lower lung function, the higher blood pressure and the lower thyroxin level. Second, the hormonal effects on the motor speed were also reported with the significantly higher performance in females during the midluteal compared to the follicular phase [34]. Hence, the above mentioned factors could confound the advantage of females in psychomotor speed tests in our three middle-aged patient cohorts.

There are two possible explanations of the faster performance of females in comparison with males in psychomotor speed tests. The smaller female brains may process simple information faster due to shorter distances within neuronetworks. In addition, some data point to the larger caudate gray matter volumes in females in comparison with males [42], what may facilitate the automatization of motor and cognitive processes in a female brain.

4.4 Executive functions

Overall, we used 5 tests sensitive to executive functions in our studies, and performance on two of them was different in the males and the females. One of the latters, i.e. Delayed Alternation Test, is a tool sensitive to orbital frontal cortex dysfunction, and in our Study 3 the females outperformed the males on this test. The matter was that the males tended to choose the same option, *i.e.* gave more 'perseverative' responses in comparison with the females.

The gender effects on the performance on the Delayed Alternation test were rarely studied, and Esposito and colleagues [43] did not find intergroup differences on the performance on DAT between males and females. No gender effects on the similar Object Reversal Test were found in the adult or adolescent cohorts in the studies by Overman [44]. Moreover, the latter research group reported the significantly better performance of the males on the other orbitofrontal test, *i.e.* Iowa Gambling Task, in comparison with the females.

Stoltenberg and colleagues [45] found no gender differences in the performance on the total result of the Iowa Gambling Task. Nevertheless, the females performed significantly better in the first part (block) of the test and significantly worse in the last (fifth) block of the test in comparison with the males in the latter study. Stoltenberg and colleagues concluded that the decision-making under ambiguity during the first block of the Gambling Task and the decision-making under risk during the following 2 – 5 blocks were regulated by different neurophysiologic mechanisms, which favored the females and males differently. Overall, the DAT is more similar to the first block of the Gambling Task and probably loads on the 'decision-making' under ambiguity, and therefore the advantage of the females over males in our study is logical.

The finding of the excess of non-perseverative errors on the WCST in males in the other study of ours is difficult to interpret. Interestingly, that the male cohort with the worse performance on DAT performed WCST as well as the females. Overall, non-perseverative responses are not considered to be a sign of the prefrontal cortex dysfunction, as in contrast to perseverative responses on DAT.

5 Conclusion

The most consistent pattern of gender differences with the advantage of females in verbal fluency and psychomotor speed tests and the advantage of males in the visuospatial reconstruction test was observed in the psychiatric patient cohort of reproductive age (mean age – 31 years). Our data are consistent with the previous findings of prominent hormonal effects on the performance on verbal fluency, visual rotation and motor speed in females. Nevertheless, the partial gender effects on cognitive functioning with the advantage of females on Digit Symbol test or the advantage of males on Block Design test were observed in some of older cardiologic patient populations as well. The inconsistency of gender effects on the cognitive performance in older patient populations may be the consequence of the concomitant effects of aging and pathological processes on brain functioning, which may confound the gender effects. Overall, these findings support the recommendation to analyze the neuropsychological data of females and males separately, especially when using tests with high sensitivity to gender effects in young and hormone-replacement therapy patient populations.

Conflict of interest

The authors declare that they have no conflict of interest.

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All authors have read and equally contributed to this article.

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