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Original Articles

PROCESSING SPEED AS AN ENDOPHENOTYPIC MARKER OF PARANOID SCHIZOPHRENIA

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Summary

Schizophrenia is associated with basic neurocognitive deficit – ineffective space-time information assessment, leading to ineffective judgment and planning of behaviour. Our study aimed to examine and compare the psychomotor speed and number of errors in patients with paranoid schizophrenia (PS), first-degree relatives (FDR) and healthy controls (HC). One-hundred-eight patients with PS, 58 with FDR and 60 HCs were examined via Trail Making Tests (TMT) A and B. The influence of other additional factors as The Positive and Negative Syndrome Scale (PANSS), demographics and education were additionally assessed for PS. Statistical analysis was done using Excel 2010, Statgraphics 5.0+ and SPSS 20. All results were interpreted at 95% confidential level. PS showed most unsatisfactory performances on TMT A and B, as compared to others (p=0.0001). However, FDR differed from HC only in TMTB performance (p=0.0241). The most significant impact in PS group included ageing, education, PANSS and negative syndromes, and syndromes of disorganization. PS showed a significant decline of psychomotor speed and executive functioning, although FDR had average results in TMTB, compared to PS and HC. The above results determined both detentions as endophenotype markers for PS. Additional risk factors for decline include ageing, low education and high PANSS results.

Key words: paranoid schizophrenia, endophenotype, processing speed

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Introduction

Studies on cognitive symptoms have been required because of their high predictive value for skill development, solving social problems and their impact on the functional outcome in society [1-3]. The modern conceptual models have considered paranoid schizophrenia (PS) as a consequence of a baseline neurodegenerative deficiency [4,5]. Its nature lies in an inefficient spatial and temporal assessment of information and experiences, as well as the formulation of ineffective decisions and plans to regulate a patient's behaviour in his/her everyday life at different levels. Cognitive impairments affect virtually every aspect of functioning, hamper a patient's ability to get engaged

in real tasks and influenced their functional outcome [6]. Cognitive changes are known to be developed at the early stages of the disease and even before its first symptoms [7-9]. They remain rather stable over time, have a significant impact on the social function outcome of the patients [10], and are seen in relatives, although at a lower level of manifestation [7].

Neurocognitive dysfunction has been considered as the right candidate for endophenotype in PS. Furthermore, the cognitive deficits are closely related to the genetic susceptibility to the disease by fulfilling the baseline criteria for "endophenotype".

Numerous researches have referred to processing speed, which, judging by the "golden standard" of neurocognitive studies in psychic pathology, has been one of the essential characteristics. Researchers have assumed that processing speed (speed of mental processes) is their own speed for solving cognitive tasks for a limited time as well as the effectiveness of visual and motor coordination in performing similar tasks [11-13]. The modern concept of executive functions includes the processes of planning and organizing mental activity, maintaining active attention and feedback, cognitive mobility, and resistance to interference.

Trail making test A and B (TMTA and B) are considered representative of the processing speed of information. It is highly dependent on the psychomotor speed and on the visual search ability.

Our study aimed to compare the processing speed and the executive dysfunction of patients with PS, first degree relatives (FDR) and healthy control (HC). It was suspected disorders not only in the patients but also in their relatives were present, and prefrontal dysfunctions were expected in both groups.

Material and Methods

A total of 226 persons were studied during the period 2017-2018, at First Psychiatric Clinic of Dr Georgi Stranski University Hospital in Pleven. The subjects we examined subjects were divided into three groups: 108 patients with PS (66 males and 42 females, mean age 38.86±10.02), 58 FDR (30 males and 28 females, mean age 36.71±11.74) and 60 HC (37 males and 23 females, mean age 35.68±11.36). The selection criteria for the PS group included regular and dose-adequate second-generation antipsychotic treatment, a stable state during the last 3 months, significant disease symptoms (measured at least mild on Positive and Negative Syndrome Scale – PANSS[15]) and with disease severity measured at least mild on Clinical and Global Impression [16]. All the subjects in the FDR were mentally healthy subjects with FDRs suffering from PS. The HC group included mentally healthy subjects without a family history of psychiatric disorders. The exclusion criteria for the study were any presence of another brain, mental disorder or mental retardation, any presence of moderate or severe somatic diseases or sensory deficits, and drug or alcohol abuse. All participants had to be right-handed (according to the Scale of Edinburgh [14])

After giving their informed consent, all patients underwent full somatic and neurological examinations, as well as clinical interview and those eligible for the study fulfilled TMT A and B.

The statistical analysis was based on descriptive, correlation and regression analysis. For intergroup comparisons, Mann-Whitney U test was used using SPSS 20.0 and Statgraphics 5.0+, as well as Excel 2010 package. All results were interpreted at a 95% confidence level.

The study pattern, the Informed Consent Form and the diagnostic and assessment tools used were approved by the Research Ethics Committee at the Medical University – Pleven. None of the procedures set in the study posed a risk to the life and health of patients.

Results

Demographic data

Table 1 shows the demographic characteristics of the individual groups of ES. The three groups had similar demographic features and were comparable (Table 1).

The duration of PS was on the average 12.8±8.2 years. The mean PANSS score was 71.8±5.1p.

TMTA and TMT B data

TMT test results are presented in Table 2. The patients differed from the FDR and HC

in both tests; whereas the HC and FDR were only distinguished by the time of doing the test TMT-B (focused attention and ability to switch between mental patterns).

TMT A Performance

The PS group was statistically different in terms of speed and quality (number of errors), as compared to FDR and HC. PS and FGR statistically differed in both indicators: processing time (U=-5.544; p=0.001) and the number of errors (U =-2.964; p=0.003). The errors, although available in the PS group, were relatively little. Only 14.81% of 108 patients had made 1 or 2 errors.

TMT B performance

The PS was statistically different in terms of speed and quality (number of errors) compared to FDR and HC (Table 2). PS performed TMT-B on the average for 110.4 sec. and made 3 errors on the average. Fifty-three subjects (49.07%) of the PS groups made more than 4 errors. The group of PS and FDR statistically differed in both processing time (U=-7.170; p=0.001) and the number of errors (U=-5.019; p=0.001). We found statistically significant differences in the performance of TMT B when comparing FDR and HC. FDR made the test for 66.38 sec, with an average of 1.19 errors while the HC group did the test 60.12 sec. with an average of 1.08 errors. HC and FDR did not show any differences in the results of TMTA (p> 0.05), but they significantly differed in TMT B (p = 0.0241), because HC had a better score than them.

Additional factors impact on the results of both tests in patients with PS.

TMT A performance

Education had an effect on the processing speed (F = 5.44; p = 0.0057) and number of errors (F=10.44; p=0.0001). For the PS group, primary education was related to worse performance of the test (p=0.0001). The family history affected only the number of errors, but not the speed of execution. Age influenced the speed of execution (rr=0.29; p=0.020), but not the number of errors p>0.05. No gender-related differences were found. The duration of the disease affected only the number of errors in TMT A (rr=0.28; p=0.0039), but not the time for completion. The overall PANSS score had an impact on the execution time (rr=0.26; p=0.0077) and the number of errors (rr=0.29, p=0.0021), the negative symptoms (rr=0.23; p=0.0193); (rr=0.38; p=0.0001) and the symptoms of

Table 1. Demographic data (age, sex and formal educations) of patients with paranoid schizophrenia, first degree relatives and healthy controls

Groups	PS	FDR	HC
N=	108	58	60
Age (years)	38.86±10.02	36.71±11.74	35.68±11.36
Sex (males:females)	66:42	30:28	37:23
Formal education (basic education 8 years; middle education 9-12years; high education>12years)	24:53:31	4:33:21	7:35:18

*PS paranoid schizophrenia, FGR – first degree relatives, HC – healthy controls; y-years

Table 2. Difference between TMTA and TMT B test performances between patients with paranoid schizophrenia, first degree relatives and healthy controls

Type	PS	FDR	HC	$P_{(PS-FGR)}$	$P_{(FGR-HC)}$
TMTA (sec)	47.87	32.88	33.75	0.0001	>0.05
TMTA err.	0.19	0	0	0.003	NS
TMTB (sec)	110.04	66.38	60.12	0.0001	0.0241
TMTB err.	3.0	1.19	1.08	0.0001	>0.05

*TMT-A (sec)-TMT-A seconds; TMT-A err.- errors; TMT-B (sec)- TMT-B seconds; TMT-B err.-TMT-B errors

disorganization (rr=0.33; p=0.0005); (rr=0.32; p=0.0008), but not on the positive symptoms (p>0.05).

TMT B performance

In our study, age affected both indicators negatively: processing speed (rr=033; p=0.0006) and the number of errors (rr=0.19, p=0.0450). Females performed better than males (p=0.0302) for the time of processing but not by the number of errors. The higher level of education was associated with better scores for TMT B in terms of speed (p=0.0001) and fewer errors (p=0.0001). The duration of the disease was associated with an increase of the time of processing in TMT-B (rr=0.30; p=0.018), but not on the number of errors. The severity of PANSS symptoms had a negative impact on both processing time (rr=0.40; p=0.001) and number of errors (rr=0.28; p=0.0035). The positive symptoms were only reflected in the increase of the processing time (rr=0.27; p=0.0052. The deepening of the negative symptoms resulted in a long time of processing (rr=0.45, p=0.0001) and a greater number of errors (rr=0.31, p=0.0010). The higher severity of the disorganization symptoms prolonged the processing time (rr=0.44; p=0.0001) and increased the number of errors (rr=0.29; p=0.0023).

Discussion

The patients with PS did significantly worse the processing speed tests. They gave way to FDR and HC in speed and quality (number of errors) in performing such tasks [12].

TMT A performance – processing speed

PS performed TMT A for a time below the population standards, however. No statistical difference was found between FDR and HC achievements. These data are consistent with other studies [17, 18]. Klemm et al. (2006) [19], however, found a statistically significant difference in TMT A performance between FDR and HC. Primary education had a negative effect on TMT A test performance in all groups. The family history affected only the number of errors, but not the processing speed. Our results in this aspect were consistent with the study of Ashendorf L. et al. (2008) [20]. Age had an influence on the processing speed but not on the number of errors in the three studied groups. There were no gender differences in TMT A performance, and no such differences have been found by other authors [12,18], except in the study of Giovagnoli A. (1996)[21]. Only in that study, the females did worse than the males. The disease duration only affected the number of errors in TMT A, but not the time for completion. The overall PANSS [15] score, the negative symptoms and the symptoms of disorganization affected the performance of the test, the implementation time and the number of errors, but not the positive symptoms. Our findings were consistent with those reported in other studies [22, 23]. Because of the similarities between most of the research data and our results, that domain is currently unsuitable for an endophenotypic marker of PS.

Switching between mental patterns - TMT B

The PS group was statistically different in terms of speed and quality (number of errors), as compared to FDR and HC (Table 2). The study of Mahurin R. et al. (2006)[24] has revealed that the deviations in the completion time are related to the visual scan, while the working memory and the executive functions are associated with TMT-B errors, indicating that both fall into different neuropsychological domains, suggesting a different clinical interpretation. Kopp B. et al. (2015)[25] have demonstrated that the number of errors but not the completion time of TMT B is related to frontal lesions on the right. Errors are a more sensitive indicator of dorsolateral prefrontal regions dysfunction, as suggested initially by Stuss et al. (2002) [26]. These results are consistent with our research, revealing that the severity of PANSS [15] symptoms affected both the time of processing and the number of errors negatively. The performances of TMT are associated with the activation of the dorsolateral and medial prefrontal regions [26]. Fujiki R. et al. (2013) compared the changes in oxy-Hb levels, during the implementation of TMT between patients with PS and HC, and have found deleterious lateralization in the PFC region and hypoactivity leading to ineffective performance of TMT in PS [27], as confirmed by other studies [28-31].

The results of functional magnetic resonance technique have indicated that TMT B, in particular, provokes bilateral activation in the prefrontal cortex and the premotor zone. Ageing is associated with reducing inter-hemispheric asymmetry and changes in activation patterns, which is associated with an additional need for a resource for inhibitory control [32]. In our study, the PS and FDR groups statistically differed in TMT B processing speed and number of errors. TMTB disturbances in the PS group have been confirmed by almost all studies [31,33,34]. For the successful implementation of the TMT B task, it is essential to perform the short periods of planning in parallel with connecting the elements. The worse performance of TMT B by patients with PS was associated with the inadequate planning of the sequence and was related to an executive deficiency. Unlike us, Dollfuss et al. (2002) did find any difference in TMT-B results between FDR and PS [35].

The comparison of FDR and HC revealed statistically significant differences in TMT B performance. Controversial results have been reported in the literature regarding the adequate performance of TMT B by FDR [35-37]. In our opinion, at TMT A, the FDR group coped with the task by using more cognitive reserves, while at TMT B, they had already demonstrated disturbances. It showed that the cognitive reserve was enough for them to perform more manageable tasks, but for more complex ones, this cognitive reserve was insufficient. It might be possible to inhibit the previous stimulus slower and that to delay them over time. That complies with other studies [17,18]. FDRs do not achieve good results at the vertebral fluency and TMT-B tests, but they usually perform well at the Wisconsin Card Sort Test or TMT A. According to Klemm et al. (2006)[19], focused attention and cognitive flexibility are indicators of the genetic vulnerability of schizophrenia. However, only a few studies have demonstrated lower FDR scores [19,38], as compared to HC. Almost all researches [26,40] have provided a clear distinction between PS and HC, but there are also ones that have distinguished between FDR. In an average sample of the Indian population, Bhatia T. et al. (2009) [18] have found no statistical difference between FDR and PS in their TMT B results. The subjects with PS and their FDR have shown lower scores in TMT B, compared to the HC. In conformity with our research, Klemm et al. (2006) [19] have also found statistically significant differences in the TMT A and B performances of FDR compared to the HC. In these studies, the FDR group performed worse than HC, suggesting that TMT B might be a marker of schizophrenia vulnerability. In other studies [33, 40], it is reported that the time required to complete TMT B by the FDR is intermediate between PS and HC we found.

Similarly to us, Klemm et al. [19] have found that females achieve better TMT B speed results than males, though with the same number of errors. The higher level of education is associated with better TMT B performance. There have been many studies where age has been found to have a negative effect on the performance time of TMT [41,42, 43]. However, few authors have failed to find such a relationship [44]. The number of errors is less sensitive to the subtle age differences than the completion time [20, 45]. Errors might not become significantly more with ageing and thus be a constant value throughout the entire life. In analyzing the factors related to the disease, it is evident that family history does not affect the test performance. The age of the disease onset did not affect the TMT-B performance either. The duration of the disease was associated with an increase of the performance time of TMT B, but not on the number of errors, confirming the proposition of Ashendorf L. et al. (2008) [20] that the number of errors is relatively constant over time and reflects a deficit of the executive functions.

The disease severity, according to PANSS [15], affects the TMT B processing speed and the number of errors. The positive symptoms have an impact only on the time increase but not on the number of errors. The worsening of the negative symptoms and the symptoms of disorganization both result in longer execution time and a more significant number of errors. According to Bilder et al. (2000) [46], the negative symptoms and those of disorganization are associated with neurocognitive deficits, whereas the positive symptoms do not give neurocognitive impairments. According to MahurinR. et al. (2006) [24], the errors in TMT B are

related to the symptoms of disorganization. The cognitive functioning and negative and positive symptoms correlation seem to be dependent on the sensory modality that engages the cognitive task

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Conclusions

The impaired achievements in TMT-B might be a direct consequence of an isolated deficit in the executive functions or an indirect manifestation associated with a more extensive cognitive impairment such as reduced focused attention. The higher susceptibility to interference and reduced inhibition of the previous stimulus might be markers of general familial vulnerability to schizophrenia [19].

Our results have shown that TMT scores might reflect a characteristic feature of the disorder and revealed a cognitive flexibility deficit as part of the executive functions. We found that FDR group work slower, from an early age. The test could be used along with other tests to identify subgroups of subjects at high risk of PS. FDR performed worse than HC, suggesting that coping with TMT-B might be a marker of vulnerability in PS.

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