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What specifically contributes to disturbed non-verbal fluency in patients with bipolar disorder: Ineffective performance initiation, slowed processing or lack of the execution strategy?

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A B S T R A C T

The study aimed at identifying the cognitive and clinical determinants of impaired design fluency in bipolar patients, with special reference to processing speed and performance strategy. A sample of bipolar disorder patients (BD, $n = 45$) and matched healthy controls (HC, $n = 42$) underwent the assessment of figural fluency, cognitive and manual speed, cognitive effort and affective state. An electronic version of design fluency test was applied, enabling assessment of performance speed, execution strategy and spontaneous fluctuations in production efficiency. Additional clinical variables were also controlled. BD patients produced significantly less unique designs, performed slower, utilized less effective strategy, their ability to concentrate designs production in the initial phase of performance was significantly reduced compared with HC. Regression analysis revealed that in BD patients design fluency main outcome was significantly predicted by slowed creation of designs and the number of hospitalizations, while in the HC group, the main fluency result was predicted only by the executive strategy indicators. Our study showed that non-verbal fluency in BD group was determined by essentially different neuropsychological functions than in healthy controls. Obtained findings confirm that cognitive slowdown should be an important goal of cognitive remediation and pharmacological interventions in bipolar disorder.

1. Introduction

It has been well documented that cognitive dysfunctions belong to a clinical picture of the bipolar affective disorder (see Tsitsipa & Fountoulakis, 2015). However, when patients with bipolar disorder (BD) are compared to their unaffected relatives and healthy controls, executive functions, working memory and processing speed seems to be most affected (Balanzá-Martínez et al., 2008; Bo et al., 2017; Bora & Özerdem, 2017). Since cognitive deficits in BD are significant predictors of patients' functional outcome (Baune & Mahli, 2015), even more than the clinical status (Jaeger et al., 2007; Dickerson et al., 2010), it is important to recognize the core cognitive disorder(s) that may contribute to neuropsychological functioning in other domains. This could then enable establishing the goal of efficient cognitive remediation that, in turn, should significantly improve patients' quality of life and functional independence.

Although patients with BD typically present with impaired attention, working memory and executive function, there is evidence that the delayed information processing might be responsible for these patients' cognitive impairment, regardless of the domain. For example, similarly to individuals with schizophrenia (Krukow et al., 2017a; Ojeda et al., 2012; Rodriguez-Sanchez et al., 2007), it has been recently shown that impaired processing speed accounts for differences in cognitive status between patients with BD and healthy controls (Antila et al., 2011; Kieseppä et al., 2005; Udal et al., 2012). Other studies in BD patients additionally show the impact of reduced fluid intelligence on the executive functions profiles in this group (Goitia et al., 2017), moreover, analogous relationships were noted in schizophrenia patients (Roca et al., 2014) and in individuals with acquired frontal lobes dysfunctions (Roca et al., 2010; Roca et al., 2013). The complex interdependencies between cognitive speed and other cognitive dimensions studied in bipolar disorder refer in particular to the relationship between executive dysfunctions and cognitive slowing. In many meta-analyzes and research studies regarding the classification of dominant cognitive impairment in patients with various affective disorders and their healthy relatives, differences in the magnitude of the effects sizes were observed in speed-dependent measures of executive functions (e.g. Trail Making Test and fluency tasks) as well as tasks in which scores are

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based on accuracy (e.g. WCST) (Bora et al., 2013; Bora, 2017; 2018; Potter et al., 2016). The results of such meta-analysis confirm a pronounced speed-dependent executive function deficit in patients with major depression and BD. Therefore, it seems particularly important to investigate whether this speed-dependent executive deficit is a primary consequence of impaired executive processing or could be accounted for by cognitive slowing.

One of the cognitive dimensions so far poorly studied in the BD group is design/figural fluency that engages both executive function and processing speed. The design fluency is the ability to create as many line drawings as possible within a given time period (e.g. 60 s) without replicating any design (Ross et al., 2003). Figural fluency tests have been used in neuropsychological diagnosis most often to detect frontal dysfunction characterized by a high amount of perseverative errors and diminished productivity (very few unique designs) (Lezak, 1995; Ruff et al., 1994). The interpretation of design fluency tasks is not burdened with issues such as lexico-semantic memory, raised in the context of verbal fluency tests (Raucher-Chéné et al., 2017). Also, according to Suchy et al. (2003), in comparison to verbal fluency tasks, figural fluency, as assessed by the Ruff Figural Fluency Test (RFFT, Ruff, 1998), places greater demands on executive processes because the figural fluency test requires the ability to cope with the uncommon type of stimuli.

Several studies have confirmed design fluency deficit in the groups of BD patients. Pålsson et al. (2013) applied the design fluency test from the Delis–Kaplan Executive Function System Battery (Delis et al., 2004) and found that in comparison to healthy controls patients with BD presented with defective set-shifting and cognitive flexibility. Also, Sparding et al. (2015) demonstrated that design fluency test from D-KEFS, together with other tasks assessing executive functions, working memory and attention, allowed distinguishing BD patients from healthy controls. Moreover, Jaeger et al. (2007), who focused on cognitive factors that may best predict functional improvement of BD patients 12 months after hospitalization, found that only attention and ideational fluency turned to be significant predictors of functional outcome.

Although in psychiatric disorders studies addressing the contribution of cognitive slowing to other neuropsychological deficits have drawn attention to the important role of the delayed information processing, many issues remain unresolved. For example, researches addressing this problem differ significantly in terms of utilized processing speed indicators. Specifically, some investigators used only the overall tests scores (e.g. the Digit Symbol Substitution Test – DSST) as a measure of cognitive slowness (Brébion et al., 2018), whereas others applied complex indexes covering the results of many tests (Andersen et al., 2012). Of note, although majority of research investigating cognitive speed in BD have used the DSST (see Cella & Wykes, 2013), there is still an ongoing debate about what exactly the DSST measures. Further, in comparison to the majority of studies applying the general scores of various tests, only Kieseppä et al. (2005) analyzed some dimensions of memory and learning separately, indicating that in BD cognitive slowing affects immediate but not delayed memory. Thus, it remains unknown to what extent the reduced processing speed in BD contributes to these individuals' cognitive performance.

Whereas previous research with BD investigated the contribution of processing speed to cognitive deficits using a statistical modelling, according to our knowledge, this was never directly tested, i.e. by the evaluation of the actual speed of performance. The paper version of the RFFT enables the assessment of the quantitative parameters, such as a total number of unique designs and the scope of perseverative errors (Ruff, 1998). Although attempts have been made to develop quantitative indicators of the strategies used to achieve better results in the RFFT, previous research has focused only on the executive aspect of the test performance (Ross et al., 2003). To separately evaluate the strategy of the performance and the speed of constructing the designs, it would be necessary to elaborate an electronic version of the test, enabling the assessment of most elementary aspects of the performance: (1) speed of connecting dots while creating designs, and (2) the strategy used, calculated based on the level of variability in the number of connections utilized to create designs (see Method section).

In previous studies investigating predictors of verbal and figural fluency in patients with schizophrenia, authors demonstrated that poor results in both types of fluency tasks resulted from a deficient initiation process, indicated by the number of correct words and designs produced during the first 15 s (Krukow et al., 2017b). Hence application of a computer version of figural fluency test in BD patients should enable controlling for possible differences in the dynamic profiles of designs production changes over the time.

Because BD patients typically present with impaired executive functions (Dickinson et al., 2017) and slower cognitive processing (Mur et al., 2008), the main goal of this study is to identify if poor design fluency seen in this population is mainly driven by executive deficits, cognitive slowing or both. We assume that, similarly to individuals with schizophrenia, BD participants will present with a defective initiation resulting in less efficient performance during the initial part of the task. Further, we suspect that, in comparison to healthy controls, individuals with BD will use less efficient strategy to perform the task and that their information processing speed, as indicated by the speed of connecting dots to create a design, will predict the total number of unique designs better than in healthy controls, also after controlling for such variables as motor speed and/or cognitive effort.

2. Methods

2.1. Participants and procedure

The following clinical and demographic inclusion criteria for the BD participants were applied: nosological diagnosis of bipolar disorder according to DSM-5 criteria carried by certified psychiatrist, clinical remission state (Hypomania Check List, 32 R1 version [HCL-32] (Angst et al., 2005) score ≤ 14, and Beck Depression Inventory ≤ 16 (Beck & Steer, 1993), results of neuroimaging (MRI) excluding the occurrence of any structural changes resulting from acquired brain injuries, at least 10 years of education, no symptoms of mental retardation, no history of alcohol or substance abuse, and a lack of any serious somatic conditions. Patients currently treated with benzodiazepines or typical antipsychotics were excluded. Healthy controls (n = 42) were matched by pairs with patients. None of the healthy participants had psychiatric problems. Other criteria for controls were similar to those applied to BD patients. The Reliable Digit Span test (RDS, Meyers & Volbrecht, 1998), with ≤ 7 points cut-off score indicating acceptable cognitive effort, was an additional inclusion criterion. The RDS is a task based on the Digit Span subtest of the Wechsler Adult Intelligence Scale-Revisited (Wechsler, 1981), and the outcome was calculated by summing the longest strings of digits repeated without error in two trials, both in forward and backward conditions (Greiffenstein et al., 1994). To control for motor speed, the Finger Tapping Test (FTT, mechanical PARINC® apparatus) was applied. During the assessment of motor speed with FTT, the maximum oscillation rate of the index fingers, by pressing the lever attached to a mechanical counter is measured, the score contains mean maximal oscillations from right and left hands. Processing speed was assessed using a computerized version of the Digit Symbol Substitution Test (eCST, a tablet software), same as in previous study (Krukow et al., 2017c), the task, as in the original DSST version, consists of the fast matching of abstract symbols to digits, within a given time limit (90 s). Computerized version allowed to preserve the standardization of cognitive measurement and to ensure a technical similarity in the performance of the cognitive speed and figural fluency test.

Subjects from both groups had generally similar demographic characteristics (see Table 1). From the initial group of 55 patients, the results of 45 were included in the final analysis. Six patients did not

Table 1
Demographic, clinical and cognitive variables in BD and HC groups.

	BD (n = 45) M (SD)	HC (n = 42) M (SD)	p-Values	η_p^2
Age (mean, years)	31.81 (9.49)	29.92 (11.11)	0.394	0.01
Gender (% male)	53.33	52.38	0.887	
Education (mean, years)	13.66 (2.52)	14.28 (2.35)	0.240	0.01
Parental education (mean, years)	11.02 (2.60)	12.12 (2.12)	0.112	0.02
Employment (% employed)	37.77	78.57	< **0.0001**	
Duration of illness (years)	4.71 (2.17)			
Number of hospitalizations	2.57 (1.54)			
Mean number of medications	1.60 (0.65)			
BD type (I/II %)	58 / 42			
Psychotic symptoms in last episode (% yes)	37			
YMRS (mean, total)	9.80 (4.78)[a]			
BDI (mean, total)	13.46 (9.06)	2.42 (0.50)	< **0.0001**	0.48
HCL-32 (mean, total)	11.15 (3.44)	4.00 (1.66)	< **0.0001**	0.59
RDS (mean, total)	10.58 (3.09)	11.61 (2.62)	0.095	0.03
FTT (mean, total)	53.33 (15.06)	48.44 (11.24)	**0.002**	0.04
Cognitive speed[b]	44.66 (16.90)	82.85 (15.37)	**0.0001**	0.59

Note: YMRS, Young Mania Rating Scale (Young et al., 1978); BDI, Beck Depression Inventory (Beck & Steer, 1993); HCL-37, Hypomania Check List, 32R1 version (Angst et al., 2005); RDS, Reliable Digit Span (Meyers and Volbrecht, 1998); FTT, Finger Tapping Test.
[a] The result available from 42 BD patients.
[b] Computer version of Cognitive Speed Test (eCST) (Krukow et al., 2017a, 2017b, 2017c), number of correctly processed stimuli.

achieve the expected level of cognitive effort, data on two patients were incomplete, and for the other two the diagnostic status turned to be unclear. Patients were treated with mean 1.60 (SD = 0.65) number of medications, which were in 55% mood stabilizers (mainly valproic acid), in 40% atypical antipsychotics (mainly olanzapine), 22% antidepressants (mainly fluoxetine), 13.3% of patients received lithium. All participants gave written informed consent. The study was performed in the 1st Department of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin, Poland. Ethical approval for the research was granted by the local bioethics committee.

2.2. Cognitive assessment: the computer version of the design fluency test

The digital version of the design fluency test, developed as a tablet application, was based on the Ruff Figural Fluency Test (Ruff, 1998). As with the original paper-pencil variant, it consists of five parts, and the task is to create as many unique designs as possible by connecting any number of dots (there are always five dots to choose from). Participant has 60 s to complete each part. Fife parts differ from each other regarding background on which the dots are placed, or in the manner they are positioned in relation to each other (Strauss et al., 2006). Each design repeated within one part of the test is treated as a perseverative error.

The strategic facet might be operationalized in two ways: firstly, by the number of utilized connections during the creation of designs. Remembering that design fluency task is time-limited, the most optimal strategy would be to generate the majority of designs with one or two quickly made connections. An ineffective approach, such as arranging figurative patterns with multiple lines, by overloading the monitoring of originality of consecutively generated designs should also contribute to an increased number of perseverations. Two additional strategies were previously described (Ruff, 1998; Ross et al., 2003), ensuring high scores in the figural fluency tests. The rotational method consisting of systematic rotation of a drawing clockwise or counter-clockwise, within the array of dots, guaranteeing that each subsequent design will be different from the previous ones. Second is the enumerative strategy that involves the systematic adding or removing one line in the subsequent designs. Both procedures have one common feature, which is the low level of variability in the number of connections utilized to create upcoming designs. In the rotational strategy, the easiest way to generate a large number of unique patterns is to perform one or two lines each time, while in an enumerative method, one line is added or removed, which is also related to the small variability in the number of used lines/connections. The individual standard deviation of the number of utilized connections during the creation of subsequent correct designs might also be a quantitative indicator showing, together with the mean number of connections, to what extent the most beneficial strategies has been implemented during the test execution (Fig. 1).

Considering the above, the computer version of the design fluency test (cDFT) used in this study enabled the evaluation of the seven theoretically-driven variables included in further analyses: (1). the total number of unique designs (TNUD), (2). number of perseverations and (3). errors ratio, (4). mean number of utilized connections, (5). intra-individual variability (iSD) of the connections number, (6). mean connecting time; a temporal interval between connecting any two dots in the task, and (7). intra-individual variability (iSD) of connecting time.

Patients and healthy controls were evaluated with the same software and hardware (Lenovo Yoga 2 tablet with the 13,3″screen, resolution Quad HD 2560 × 1440 IPS, Android™ 4.4 system), which guaranteed the standardization of the assessment. The cDFT was previously used in psychophysiological studies concerning the effectiveness of such executive functions as planning and monitoring of errors in the group of healthy adults (Borys et al., 2017). A detailed description of the computer version of the design fluency test is included in the Supplementary materials.

2.3. Data analysis and statistics

After calculating the raw results for the variables assessed with the cDFT test, several steps of statistical analyses were performed to establish final determinants of the design fluency performance separately for each group. First, demographic, clinical and cognitive side variables were compared in two studied groups using the ANOVA to identify variables differentiating the groups, controlled in further analyses. Secondly, a correlation table was prepared containing a set of relationships between the individual cDFT parameters for all participants to control for the potential redundancy of these parameters (Table 1S. in Supplementary materials). Variables significantly correlating at the level greater than 0.50 were reduced to individual parameters. After establishing the final number of analysed variables describing the execution of cDFT, the analysis of covariance (ANCOVA) has been conducted to compare groups regarding the performance of design fluency test, including side-variables significantly differing the groups (e.g.

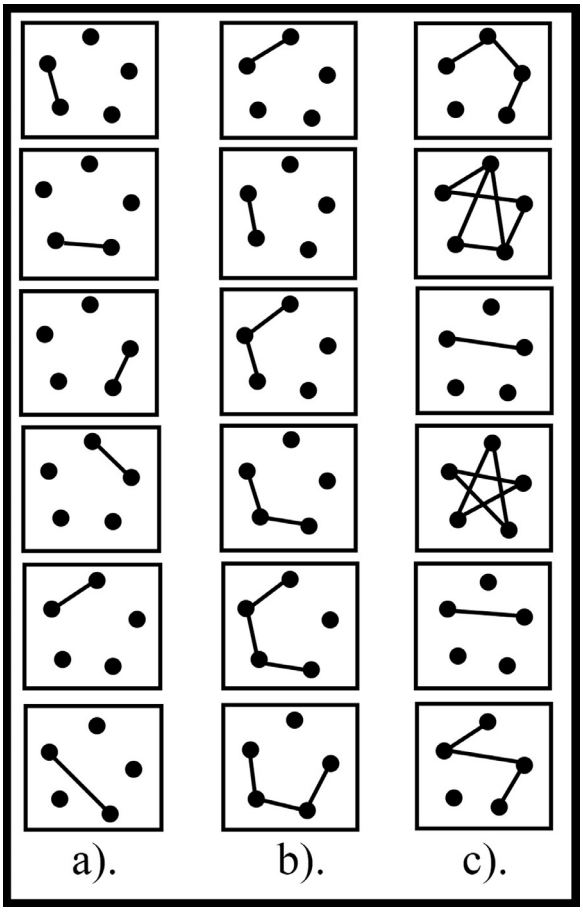

Fig. 1. Three examples of creating six consecutive designs. (a) shows very effective performance, with the high level of consistency in the number of used connections. Individual standard deviation (iSD) for the number of utilized connections in this example is 0 because every design was created with one connection. (b) An example of subsequent designs created according to the enumerative strategy, iSD = 0.89. The example (c). demonstrates the high level of variability in the number of used connections (iSD = 2.04), the performance is substantially ineffective due to lack of strategy in creating designs. The fifth design is a repetition of the third on, qualified as the perseverative error.

motor and cognitive speed) as controlled covariates. Next, the repeated measures ANCOVA was applied to verify if there were between-group differences concerning changes in the number of unique designs, errors, mean number of connections and mean connecting time ongoing over the five consecutive parts of the test, again with controlling for independent side-variables. An analogous analysis was carried out regarding the variability in the number of utilized connections and connecting time over the time of performance (2 groups × 2 halves of the task). To capture the potential fluctuations in the efficiency of designs generation over time, the period in which subjects had to generate designs (60 s) has been divided into three 20 s intervals. Again, mix-model repeated measures ANCOVA was conducted (2 groups × 3 time intervals) with η_p^2 as an effect size indicator and controlling the previously described covariates. The Tukey's test was used in post hoc analysis and Bonferroni corrections for multiple testing.

Cognitive variables (e.g. number of connections) that significantly differentiated studied groups were again used as potential contributors in ANCOVA, in which the total number of unique designs was implemented as a dependent variable. This analysis was carried out to verify whether the difference between any of the individual cognitive indicator, especially the number of connections and the connecting time was a factor significantly determining the between-group difference in the total number of unique designs. If the described procedure did not reveal the dominant contributor, then the regression analysis was performed separately for BD and HC groups, to identify the variables that ultimately determined the number of unique designs in each of the studied groups. In the regression model only these variables were included, which significantly correlated (Pearson's correlation coefficient) with the overall cDFT results.

3. Results

Overall, patients had similar demographic characteristics as controls, except for the employment status (Table 1). As expected, BD group received a higher rating in scales assessing the affective state and their results suggest that a part of BD sample were in an incomplete symptomatic remission, however, none of them obtained scores indicating the state of active clinical phase of mood disorders. Nevertheless, due to mentioned results, rates of affective state were controlled in further analyses. Patients were also manually and cognitively slower. The level of cognitive effort was similar in both studied groups.

3.1. Between-group differences in the individual design fluency test parameters

The results in Table 1S (Supplementary materials) indicate that variables such as mean connecting time and intra-individual variability of connecting time ($r = 0.82$, $p < 0.001$), as well as the number of errors and errors-ratio ($r = 0.57$, $p < 0.01$) were significantly and highly correlated, therefore, in subsequent analyses, only mean connecting time and number of error were implemented.

As shown in Table 2, BD patients produced significantly less unique designs and utilized more connections to generate designs, the number

Table 2
The intergroup comparison of individual parameters of design fluency performance with ANCOVA including results of BDI, HCL-32, FFT and cognitive speed as controlled variables.

	BD ($n = 45$) corrected means (st. error)	HC ($n = 42$) corrected means (st. error)	$F(1, 75)$	p	η_p^2
Total number of correct designs	58.44 (6.40)	108.72 (6.52)	12.77	**0.001**	0.154
Number of errors	3.40 (0.65)	4.56 (0.66)	0.79*	0.374	0.011
Number of connections M	5.09 (0.65)	3.35 (0.44)	3.58	**0.012**	0.045
Number of connections iSD	1.41 (0.04)	1.19 (0.05)	1.48	0.114	0.022
Connecting time M	1205[a] (201.74)	1143.30 (211.44)	0.02**	0.872	0.001
0–20 s interval	4.56[b] (0.65)	8.60 (0.69)	10.11	**0.002**	0.126

Note. [a] data given in milliseconds, [b] the number of unique designs produced during first 20 s of the performance.

* The intergroup difference regarding number of errors was significant after inclusion of BDI, FFT and cognitive speed, but not HCL-32 scores, as controlled variables: $F(1, 75) = 3.98$, $p = 0.041$, $\eta_p^2 = 0.049$.

** The intergroup difference regarding mean connecting time was significant after inclusion of BDI, HCL-32 and FFT, but not the cognitive speed, as controlled variables: $F(1, 75) = 4.48$, $p = 0.027$, $\eta_p^2 = 0.056$.

of designs generated in the first time interval (0–20 s.) was also lower than in HC group. The intergroup difference concerning mean connecting time was significant after controlling for affective state and manual speed ($p = 0.027$), however, this difference ceased to be significant when cognitive speed was included as a controlled covariate.

3.2. Between-group comparison of variability in the performance of the cDFT

After inclusion of such controlled variables as affective state (results of BDI and HCL-32 scales), manual speed (Finger Tapping Test) and cognitive speed assessed with digitalized version of Digit Symbol Substitution Test, there were no significant interaction effects (2 groups × 5 test parts) regarding the number of unique designs, mean number of connections, connecting time and number of errors, over the five consecutive parts of the design fluency test (all $p > 0.05$). Additionally, controlling for the same side variables, there were no significant interaction effects (2 groups × halves of the task) for the variability in the number of utilized connections and connecting time over the time of performance (all $p > 0.05$).

However, the profile capturing changes in the production of designs over time was different in each studied group; interaction effect: $F(3, 170) = 6.32$, $p < 0.001$, $\eta_p^2 = 0.202$ (significant also after Bonferroni correction for multiple tests and controlled covariates as: BDI, HCL-32, FFT and cognitive speed). Post-hoc analysis revealed that, whereas in the BD group number of designs generated in the last interval (from 40 to 60 s) was significantly lower than in the first interval, in HC the number of designs generated during the first 20 s was significantly higher than in all other intervals in both groups. Thus, the dynamic profile of HCs suggests that their highest efficiency was due to the performance within the first 20 s of the test. Although the production of designs in the BD group also decreased over time, production efficiency in the initial intervals was not as high as in the control group. (Fig. 2)

3.3. Analysis of potential contributors to the between-group difference in the total number of unique designs

The ANCOVA showed that after controlling for covariates such as: the number of designs produced during the first 20 s, mean number of connections and mean connecting time, the between-group difference in the TNUD remained statistically significant: $F(1, 80) = 7.93$, $p = 0.006$, $\eta_p^2 = 0.10$. However, two of the controlled covariates had a significant impact on the between-group difference in TNUD: number of designs produced during the first 20 s: $F(1, 82) = 52.02$, $p < 0.0001$, $\eta_p^2 = 0.39$, and mean connecting time: $F(1, 82) = 14.66$, $p = 0.0002$, $\eta_p^2 = 0.15$.

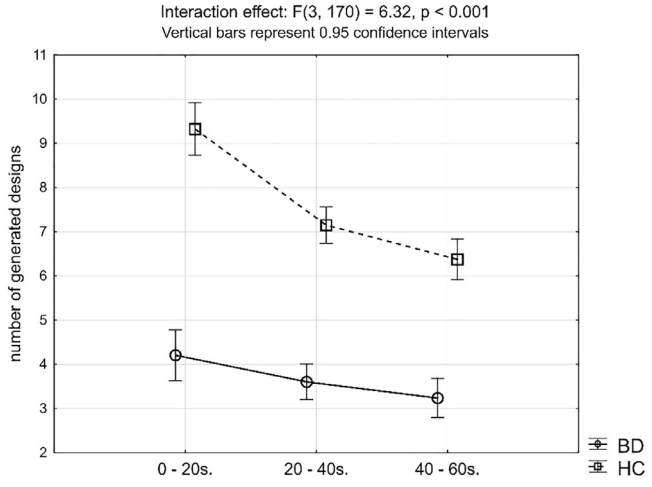

Fig. 2. Results of the group × within-profile variability ANOVA for the cDFT in BD patients and healthy controls. The figure shown mean numbers of designs generated in 20 s intervals.

Table 3
Detailed results of regression model in BD group with TNUD as dependent variable.

Independent variables	Beta	Beta St. error	B	B St. error	*t*(39)	*p*
(Constant)			92.98	12.71	7.90	< **0.001**
Connecting time M	−0.63	0.09	−0.01	0.01	−6.22	< **0.001**
Number of hospitalizations	−0.51	0.13	−3.57	0.92	−3.85	< **0.001**
Cognitive speed	−0.08	0.10	−0.10	0.12	−0.81	0.419
YMRS	−0.04	0.12	−0.11	0.27	−0.42	0.675
Number of medications	−0.12	0.09	−3.78	3.12	−1.21	0.233

3.4. Predictors of the total number of unique designs in BD and HC groups

The total number of unique designs in the BD group correlated significantly with mean connecting time (−0.74), number of hospitalizations (0.45) and with the index of cognitive speed (0.34; Table 2S in the Supplementary materials). Among all variables which correlated with the TNUD in the patients group, two proved to be significant predictors of the total number of unique designs: mean connecting time and the number of hospitalizations: $F(5, 39) = 14.79$, $p < 0.0001$, $R^2 = 0.65$, corrected $R^2 = 0.61$, estimation standard error = 12.71, $t(39) = 7.90$, $p < 0.0001$, also after controlling for YMRS score and number of medications (Table 3). Included predictors were not correlated witch each other, however, as presented earlier, intergroup differences in cognitive speed contributed to between-group differences in mean connecting time.

In HC group, TNUD correlated significantly with mean number of connections (−0.73) and the years of education (0.43). However, since both these variables were correlated ($r = 0.35$, $p = 0.022$), two separated regression models were calculated to establish dominant predictors of TNUD in HC group. Mean number of connections appeared to be a significant predictor: $F(1, 40) = 30.16$, $p < 0.0001$, $R^2 = 0.44$, corrected $R^2 = 0.42$, estimation standard error = 6.51, $t(340) = 22.50$, $p < 0.0001$ (Table 4), while years of education as an independent variable turn out to be non-significant predictor: $F(1, 40) = 3.72$, $p = 0.132$.

Mean connecting time ($\beta = -0.46$) and the number of hospitalizations ($\beta = -0.42$) were also significant predictors of number of correct designs produced during the first 20 s of the test performance in BD group: $F(2, 42) = 17.38$, $p < 0.0001$, $R^2 = 0.45$, corrected $R^2 = 0.42$, estimation standard error = 1.47, $t(42) = 13.15$, $p < 0.0001$ (Table 5), significant predictors were not correlated.

Among all controlled side variables in BD group, mean connecting time marginally correlated with total result of BDI ($r = 0.29$, $p = 0.048$). Also, there was no significant difference regarding any individual parameters of design fluency test performance between BD type I and type II subgroups (Table 3S in the supplementary materials), analogously to subgroups distinguished on the basis of occurrence or non-occurrence of psychotic symptoms during the last affective episode

Table 4
Detailed results of regression model in HC group with TNUD as dependent variable.

Independent variable	Beta	Beta St. error	B	B St. error	*t*(39)	*p*
(Constant)			140.44	21.22	6.61	< **0.001**
Number of connections M	−0.66	0.12	−6.70	1.76	−5.49	< **0.001**

Table 5
Detailed results of regression model in BD group with number of designs generated in first 20 s of the task as dependent variable.

Independent variables	Beta	Beta St. error	B	B St. error	*t*(39)	*p*
(Constant)			6.96	0.52	13.15	< **0.001**
Connecting time M	−0.46	0.11	−0.02	0.01	−4.00	< **0.001**
Number of hospitalizations	−0.42	0.11	−0.27	0.07	−3.65	< **0.001**

(Table 4S in the supplementary materials).

4. Discussion

The current study investigated specific determinants of design fluency in patients with bipolar disorder, with particular reference to the speed of the performance and the implementation of an executive strategy. As hypothesized, BD patients generated significantly less unique designs, performed slower, created figures with a higher number of connections and were less able to concentrate cognitive efficiency in the initial seconds of the task. However, although in the direct comparison patients had higher errors-ratio, after controlling for the severity of residual manic symptoms this difference proved to be non-significant.

Overall, the most important outcome of our study is the demonstration that the production of unique designs in two research groups was predicted by essentially different cognitive processes. In contrast to patients with BD, in healthy controls, the main score of the fluency test was predicted by a smaller number of used connections. This effect suggests that the executive aspect conditioned the test performed by controls (see Ruff, 1998), and that proposed quantitative indicators of the execution strategy were valid estimators of the test's overall score. Despite the fact that BD patients achieved significantly worse results regarding the applied strategy, only the speed of designs' creation proved to be a significant predictor of impaired figural fluency. The applied analyses clearly showed that slower generation of designs in BD patients is not an effect of motor retardation but rather reflects delayed cognitive processing. Reduced construction speed additionally predicted deficient initiation observed in the bipolar group. As expected, BD patients were less cognitively efficient in the first several seconds of the performance, similarly to patients with schizophrenia (Krukow et al., 2017b). However, in BD group initiation deficit has not accounted for these individuals' total performance in the figural fluency test, what additionally emphasize the impact of slowed performance on impaired fluency in the bipolar group.

The findings of this study demonstrate complex relationships between cognitive speed and other dimensions of information processing in a bipolar sample. However, although incorporation of the DSST score in the intergroup comparison of the total number of unique designs reduced the scope of statistical difference, this difference remained significant. The fact that the difference remained significant might be explained by an evident dissociation concerning cognitive functions that influenced the overall results in two studied groups.

The study confirmed the relationship between selected aspects of the clinical picture of BD and the cognitive functions. This applies first of all to affective states and the number of psychiatric hospitalizations associated with the relapse of the disease, and to the relationship of manic symptoms with perseverative errors and depressive symptoms with slowing of designs creation. These results are generally convergent with previous findings confirming that depressed mood is associated with decreased mental speed (Hammar & Årdal, 2009; Kalb et al., 2006; Potter et al., 2013; Tsourtos et al., 2002). Some authors suggest that the decreased mood, by induction of the ruminations, leads to an overload in the attentional and working memory systems, which in turn affects the speed of cognitive performance (Payne & Thompson, 2015). However, there are also findings showing that depressed mood might impede the cognitive performance by extending the time of conceptualization or decision processes made during the task execution (Kuhbandner et al., 2009). The associations between manic symptoms and executive dysfunctions, including response control, is also consistent with previous reports (Clark et al., 2001; McGrath et al., 2001; Vrabie et al., 2015). The number of hospitalizations additionally influenced the figural fluency outcome in bipolar patients. Although conclusions of other investigations considering the potential impact of previous episodes on cognitive functions in this population are contradictory (Demmo et al., 2016; Vrabie et al., 2015), the main reason for hospitalization is the recurrence of a mood disorder, and it has been demonstrated that the cognitive status of BD patients deteriorates due to subsequent disease relapses (López-Jaramillo et al., 2010). Our group of patients was heterogeneous in terms of the type of affective disorder (BD type I and II) and the occurrence of psychotic symptoms during the last affective episode, however, it did not affect the score obtained by patients in the cDFT. These results are in accordance with current studies (Demmo et al., 2016; Pålsson et al., 2013; Trisha et al., 2018) and meta-analytical inspection (Dickinson et al., 2017) which have found no empirical evidence indicating a significant effect of psychotic symptoms on the level of neuropsychological deficits in patients with bipolar disorder nor substantial differences regarding executive functions between BD type I and II patients, although such relationships were described in earlier investigations (Hsiao et al., 2009; Kung et al., 2010).

According to our knowledge, this is the first study focused on specific cognitive and clinical aspects impeding the design fluency in bipolar patients. The assumed impact of cognitive speed on figural fluency was assessed directly, not by the statistical modelling. Additionally, it has been shown that decreased performance speed was a significant predictor of design fluency in bipolar group, regardless of manual speed as well as cognitive effort. According to Correa-Ghisays et al. (2017), long-lasting dysfunctions of manual motor speed are evident in bipolar subjects, even after controlling for many clinical and sociodemographic variables. Therefore, controlling for manual speed in our research seems to complement a methodological gap present in other studies.

The impact of reduced processing speed on other cognitive domains seems to be relatively universal and does not affect only BD patients. As indicated earlier, significant contribution of delayed information processing to other cognitive deficits has also been reported for individuals with schizophrenia (Ojeda et al., 2012; Rodriguez-Sanchez et al., 2007), but also in the vascular brain injury (Su et al., 2015), after pediatric traumatic brain injury (Gorman et al., 2015) and with multiple sclerosis (Leavitt et al., 2014). These findings have potentially significant implications for the clinical assessment of cognitive functions, particularly when time-limited tests are administrated. Cognitive speed, both in healthy individuals and in various clinical groups, including bipolar disorder, was repeatedly associated with the structural and functional properties of the white matter (Chopra et al., 2018; Kochunov et al., 2016; Krukow, 2014; McKenna et al., 2015; Turken et al., 2008). Current studies addressing the influence of pharmacological treatment on the nervous system in bipolar disorder confirm the significant effect of lithium therapy on the improvement of the white matter microstructure (Berk et al., 2017; Kafantaris et al., 2017). These findings are of considerable clinical importance since they suggest the opportunity to modify the cognitive disorders in BD by pharmacological treatment ameliorating the neuronal substrate of cognitive speed, which might lead to a generalized impact on other aspects of information processing. Although this assumption seems promising, future studies are clearly needed.

This study has also several limitations that need to be considered. First, we have administered an experimental variant of the computer version of the design fluency test without a fully developed psychometric background as it is in the original Ruff's test (Łojek & Stańczak, 2005; Ruff, 1998). Hence, the use of the experimental version of the test

partially limits the possibility of generalizing the results to other psychometric tests measuring non-verbal fluency. However, using a computerized task allowed us to capture the dynamic aspects of its performance, especially such variable as connecting time. Second, the potential effect of psychopharmacological treatment was only partially controlled. Patients engaged in this study received various types of medications that made it impossible to estimate the unified quantitative equivalent. Since it was assumed that the number of received medications might be indicative of the extent to which a given patient required psychiatric treatment, this index was controlled in the regression analysis. However, future studies should control for the potential impact of the pharmacotherapy, for example by including participants receiving only lithium in a monotherapy (Mur et al., 2008). Third, one of the significant predicates of the total number of unique designs in the clinical group was the number of hospitalizations, and, what needs to be mentioned, not all patients met the criteria of full euthymia. This effect suggests that in subsequent studies focused on the contribution of the cognitive slowdown to other neuropsychological dysfunctions, first-episode individuals should be included to rule out confounding factors associated with prolonged mental illness. Thus, a replication study with a bipolar group minimally burdened with clinical features interfering with the outcome of the neuropsychological assessment is warranted.

Our study confirms the significant impact of cognitive slowdown on speed-dependent executive function, in this case design fluency, in the group of patients with bipolar disorder. This influence was measured directly, not by statistical modelling, which is an additional argument for recognizing the cognitive slowdown as an important goal for both cognitive remediation and pharmacological treatment, with particular emphasis on the influence of lithium on the white matter, which might be considered the main neuronal substrate of fast information processing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.11.012.

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