Cognitive Deficits in Euthymic Patients with Bipolar Disorder: State or Trait Marker?

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Abstract:

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Cognitive deficits have been demonstrated in people in the euthymic phase of bipolar disorder. This cross-sectional study compared euthymic bipolar disorder patients (N=30) with never psychiatrically ill controls (N=30) on a neuropsychological test battery containing tasks of executive function, the Wisconsin Card Sorting Test (WCST), attention and working memory, Digits Forward and Backward, and speed of information processing, Digit Symbol. Scores on the Mini Mental State Examination (MMSE) and Vocabulary Test did not differ between the groups. The bipolar group were significantly impaired compared to controls on various indices of executive function on the Wisconsin Card Sort Test and on the Digit tests. The impaired performance on the Digit tests, but not the WCST, was significantly associated with medication status, notably prescribed benzodiazepines. There was no significant effect of severity or course of illness on performance. The findings support the hypothesis that impairments in executive function are present between illness episodes in bipolar disorder, and so are not simply state markers.

Key words: Bipolar disorder, cognition, executive function, mania, depression

INTRODUCTION

Patients with Bipolar Disorder present with cognitive deficits, both during affective episodes and euthymic periods. The exact nature of cognitive deficits has been debated; some studies have suggested generalised deficits (Coffman et al., 1990; Johnstone et al., 1985; Kessing 1998; Tham et al., 1997), while others have suggested specific deficits in executive functions (Ferrier et al 1999; Rubinsztein et al 2000) . Systematic review and meta analysis have also given diverse results. A systematic review by Tsitsipa et al (2015) concluded that the neurocognitive deficit in bipolar disorder encompasses almost all neurocognitive domains. They suggested that one reason for this could be the heterogeneity of the bipolar group. The authors also discuss that there may be a continuum starting from those patients who might not differ from healthy controls to those who do not differ from patients with schizophrenia. Similar pattern of different cluster of bipolar patients with varying cognitive impairment is reported by Roux et al (2017). The authors in a cross sectional study on euthymic patients with bipolar disorder identified four distinct cognitive clusters. Two of the clusters had average global cognitive performance (with either high or low verbal memory) while the other two clusters had either above or below average global cognitive performance. In contrast to the more generalised deficits found by Tsitsipa et al (2015), a meta-analysis by Torres et al (2007) found that compared to a healthy control group, euthymic bipolar patients had specific deficits in attention, processing speed, executive function along with deficits in episodic memory. Bostock et al (2017) in their systematic review of cognitive functions in euthymic patients of bipolar disorder also reported specific impairments in cognitive domains of executive functions, attention span and verbal memory.

The origin and course of cognitive deficits remains unclear. It's possible that the cognitive deficits in bipolar disorder may be predominantly neurodevelopmental in nature and represent a core primary characteristic of the illness which is evident in first-episode bipolar patients and do not progressively worsen in most patients (Bora et al., 2015; Bora et al., 2017; Samamé et al., 2014). Other reviews have suggested that cognitive functions worsen with illness progression (Robinson et al., 2006; Cardoso et al., 2015). The possibility of kindling secondary to neurological damage caused by recurrent episodes of bipolar illness has been hypothesized (Kessing et al., 2005). There is a suggestion that this may be manifested through cognitive deficits. It is therefore, still not clear whether the cognitive

deficits represent a neurodevelopmental trait of Bipolar Disorder or are secondary to psychopathology that develops after the onset of mood state

We carried out this study to add to the existing evidence on the nature and extent of these cognitive deficits as they can have significant and enduring impact on functioning of the individuals affected by bipolar disorder. We tried to address some of the shortcomings of previous studies by having stringent criteria of euthymia and trying to control for the effect of medications and course of illness.

METHODS

Participants

This cross-sectional study compared adults in the euthymic phase of bipolar disorder with never-psychiatrically ill controls. The patient sample was recruited from consecutive patients attending for psychiatric follow-up consultations at King George's Medical University, Lucknow, India. The control participants were recruited from the spouses and friends of patients. The patients and control participants were not matched individually for their socio-demographic characteristics but an effort was made to match the two groups overall. However, recruitment of the control group participants from spouse and friends ensured an overall match between the two groups on sociodemographic factors such as age, sex, education, socio-economic status and life style factors.

Inclusion and Exclusion Criteria

Cases were diagnosed, by a Professor of Psychiatry, as having Bipolar disorder, in euthymic state for at least 1 month (American Psychiatric Association DSM IV, 1994). For inclusion in the study, cases were required to have had at least 2 mood episodes in the previous 5 years, minimum 8 years of education and be aged between 20 and 50 years. Patients were excluded if they had any comorbid diagnosis, had electro convulsive treatment (ECT) in the last 6 months, or were experiencing significant side effects on the prescribed medicines. Controls were excluded if they had any history of psychiatric illness or a family history of psychiatric illness in a first-degree biological relative. Both cases and controls were excluded if there was history suggestive of other disorders which can cause cognitive impairment (such as,

neurological or cerebrovascular disorder), had a history of recent psychoactive substance use or a history of harmful use or dependence (except tobacco), they were not able to complete the assessment due to any medical problem or if they had a score of more than 7 on Hamilton Rating Scale for Depression (HRSD) or Young Mania Rating Scale (YMRS).

Procedure

All subjects gave informed consent. A semi-structured proforma containing a detailed psychiatric interview was used to elicit information from patients and controls. A detailed physical and mental state examination was done for all the patients and controls. Side effects of medicines were documented using the semi-structured proforma. History of past episodes was confirmed using the hospital records, where available. It was ensured that if the patients were prescribed benzodiazepine medications, they had not taken it on the day of evaluation. Assessments following diagnosis were done by one of the authors, who was a resident doctor in Psychiatry at the time of the study and was not blind to the diagnosis of the patient. All the participants completed a series of neuropsychological tests administered individually. The whole assessment was carried out on the same day when the mood rating scales were administered (the YMRS and HRSD) to ensure that we had a current measure of mood. Approval for the study was given by the ethics committee of King George's Medical University, Lucknow, India.

Measures

Following neuropsychological tests were administered to each participant.

Wisconsin Card Sorting Test

Wisconsin Card Sorting Test (WCST) (Revised and expanded version, Heaton et al., 1993) is a measure of executive function requiring the ability to develop and maintain an appropriate problem-solving strategy, and to shift attentional set as the rules are covertly changed.[14]

Wechsler Adult Intelligence Scale Subtests (Wechsler, 1997)

We used the Digit Forwards test, which assesses immediate verbal memory span, the Digit Backwards, which assesses both immediate verbal memory span and the ability to manipulate the information in verbal working memory, and the Digit Symbol, which assesses speed of information processing and attention.

The Mini-Mental State Examination (Folstein et al., 1975)

The Mini-Mental State Examination is a test of a broad array of cognitive functions including orientation, memory, and language. It was used to identify and exclude potential participants with early onset dementia.

Vocabulary Test (Stanford-Binet Intelligence Scale Subtest-Form L -M1960, Hindi Adaptation by Kulshrestha, 1971). The Vocabulary test was used in our study to get an approximate measure of premorbid intelligence.

Statistical Analysis

Clinical and socio-demographic data were compared using student t-tests and Chi square analyses. Neuropsychological data were analyzed using t-tests. Significance level was kept at .05 for all the analyses. To control for type 1 error due to multiple comparisons, the p value was Bonferroni corrected and the corrected p values were considered significant at .005 level (.05/8 neuropsychological variables). All data were analyzed with SPSS for windows 16.

RESULTS

Out of the 69 patients screened, 34 met criteria for inclusion in the study. Two of them did not turn up for the assessment while another 2 were subsequently excluded as their HRSD score was more than 7 at the time of detailed assessment. Thirty patients were therefore included in the study. Out of the 74 controls screened, 30 were included in the study. The patient sample in our study was 90% male (27/30). We did not make any effort to balance the gender ratio and consecutive patients who met selection criteria were included. The predominantly male composition of the patient group in this study may reflect the trend of patients with bipolar disorders attending the psychiatry outpatient department at the hospital where the study was done.

The patient and control group were comparable on socio-demographic characteristics of age, gender and number of years of education they had (table 1). Their premorbid intelligence assessed through vocabulary subtest of WAIS was comparable and they had similar scores on their YMRS and the HRSD scores (all $p>0.05$; see table 1). The patients' drug status was the same for at least the previous 2 months. No patient included in the study was diagnosed to be having any other co-morbid psychiatric disorder at the time of assessment.

Insert Table 1 here

On the MMSE, which assesses overall general cognitive ability, the bipolar affective disorder (BPAD) patient group did not significantly differ from the control group (p=.094). The patient group performed significantly worse on measures of information processing (digit forward and digit symbol substitution tests) and working memory test as assessed by digit backward test (all ps<.001). Furthermore, the BPAD patients were significantly impaired on various parameters of executive functions as assessed by the WCST: the patients group had poor conceptual ability, completed lesser number of categories, committed more errors, and made more perseverative responses and perseverative errors (all ps <.001, significant after Bonferroni correction). The patient group also made more non-perseverative errors but this difference was not significant (p=.043, not significant after Bonferroni correction). These results are shown in table 2.

Insert Table 2 here.

We were interested in understanding if the observed cognitive deficits could be explained by the medications that 25 out of the 30 patients in our study were taking. We, therefore, divided them into 2 subgroups based on their medication status. Those patients who were on medications implicated for causing cognitive side effects were placed in "Patient Meds A" group (n=13) while the "Patient Meds B" group (n=17) had either drug free patients (n=5) or those taking medications unlikely to cause cognitive side effects (see tables 3).

Insert Table 3 here

None of the patients had troublesome side effects and the dosages were well within therapeutic range. One way analysis of variance (ANOVA) analyses were carried out individually on each of the variables with the groups (Patient Meds A, Patient Meds B, Control) as between subject factor. Significant group effect was followed up by post hoc Tukey HSD test. To control for the type I error Bonferroni corrected significance level was .006 (.05/8 ANOVAS). The ANOVA analyses showed that the three groups were significantly different on the Digit Forward test, $F(2,57)=9.57$, p=.001, $\eta 2= .251$ and on the Digit Symbol test , $F(2,57)=13.48$, p=.001, $\eta^2= .321$. Post hoc test revealed that the "Patient Meds A" group had significantly worse performance on the Digit Forward and Digit Symbol tests compared to the control group (p=.001 & p=.001 respectively) and "Patient Meds B" group (p=.024 & p=.002 respectively). However, Patient Meds B" group did not differ from the control group on the Digit Forward or Digit Symbol tests (p=.298 & p=.449 respectively). On the Digit Backward test the ANOVA analysis showed a significant main effect of groups,

F(2,57)=9.24, p=.001, η^2= .245. Post-hoc test showed that the "Patient Meds A" group had significantly worse performance compared to the control group only (p=.001). "Patient Meds B" group were marginally more impaired than the control group (p=.062) but did not differ significantly from the "Patient Meds A" group (p=.157). On the measures of the WCST, the ANOVA analyses revealed a significant main effect for groups on % preservative error scores F(2,57)=5.66, p=.006, η^2= .166, where both the "Patient Meds A" and "Patient Meds B" groups had worse performance than the control group (p=.032 & p=.015 respectively) but they did not differ significantly from each other (p=.996). Similarly, a significant main effect for groups was observed on % conceptual level response F(2,57)=7.60, p=.001, η^2= .217. The Post hoc test revealed that the both "Patient Meds A" and "Patient Meds B" groups had significantly worse performance compared to the control group (p=.005 & p=.007 respectively) while they did not differ significantly from each other (p=.937). This trend of results continued on the number of categories completed scores where a significant main effect of groups was found F(2,57)=8.12, p=.001, η^2= .228. The Post hoc test revealed that both the "Patient Meds A" and "Patient Meds B" groups had significantly worse performance compared to the control group (p=.005 & p=.004 respectively) and again they did not differ significantly from each other (p=.983). However, on the % non-perseverative error scores and the % preservative response the three groups did not differ significantly, F(2,57)=2.05, p=.139, η^2= .069 and F(2,57)=4.31, p=.018, η^2= .136 respectively. A summary pattern of this result is presented in table 4.

Insert table 4 here

We were also interested in understanding if those patients who were judged to have a less severe course were more impaired on neuropsychological functions compared to those who were judged to have a more severe course. Less severe course (n=15) was defined as no more than 2 major affective episodes in the last 5 years with recovery within 12 weeks of referral for specialist treatment. More severe course (n=15) was defined as at least 3 major affective episodes in the last 3 years or 1 year of unremitting illness in the last 3 years. Similar criteria were used in a study done by Ferrier et al (1999) to define the course of illness. The basic sociodemographic characteristics did not differ significantly between the two patient groups (all ps>.28). The two groups performed similarly (all ps>.29) on measures of information processing, working memory, and executive functions (table 5).

Insert Table 5 here

DISCUSSION:

The study investigated if euthymic bipolar disorder patients show cognitive deficits on tests of executive functions, speed of information processing and attention. Compared to a matched healthy control group, the patients had deficits in the areas of immediate verbal memory span (the Digit Forwards and Backwards tests), ability to manipulate the information in verbal working memory (the Digit Backwards test), speed of information processing and attention (the Digit Symbol test) and various aspects of executive functions (the WCST). Our results are consistent with other studies; a meta-analysis by Torres et al (2007) found that compared to a healthy control group, euthymic bipolar patients had deficits in attention, processing speed, executive function along with deficits in episodic memory (Torres et al., 2007). More recent studies (Varbie et al., 2015) also supported similar findings.

It has been a lingering question in research in mood disorders if the cognitive deficits are a state marker or trait marker and /or if the cognitive deficits are secondary to the effect of medication. To investigate if the cognitive deficits present in the euthymic bipolar patients are affected by the medication status of the patients we divided the patients into further two groups. “Patient Meds A” group included those who were on medications typically known to cause cognitive impairment and “Patient Meds B” group included those who were not on any medication or on medication not known to cause significant cognitive impairment. Eight out of 13 patients in “Patient Meds A” group were on benzodiazepines, which can affect performance on cognitive tests and cause drowsiness. It was, therefore, ensured that they had not taken benzodiazepine medication on the day of evaluation. The findings showed that on measures of executive functions as measured by the WCST, the two groups of patients did not differ from each other. Both groups of patients were significantly impaired on the measures of WCST as compared to the control group. However, the “Patient Meds A” group patients were more severely impaired on tests of immediate verbal memory span (the Digit Forwards and Backwards tests), ability to manipulate the information in verbal working memory (the Digit Backwards test), speed of information processing and attention (the Digit Symbol test). The results were statistically significant on the Digits forward and Digits symbol tests. However, the difference between the two groups was not large enough to reach significance levels on the Digits backward test. The “Patient Meds A” group had comparable performance to the controls on these tests. These findings highlight the effect of medications on certain aspects of cognitive functioning in BPAD patients, especially speed of information

processing and immediate memory span. A recent meta-analysis concluded that benzodiazepines negatively affect performance on a number of cognitive domains including that of recent memory, processing speed, visuoconstruction, divided attention, working memory, and sustained attention (Crowe et al., 2017). These negative effects were present even in those who had withdrawn from benzodiazepines. Our findings hence suggest that executive function deficits as measured by the WCST are not secondary to effects of medications while other deficits could be due to the effects of medication. A number of reviews and meta-analyses have consistently shown that the residual cognitive deficits during euthymia are specific to executive functions (Torres et al., 2007; Bostock et al., 2017). Torres et al (2007) also suggested that the effects of medication do not fully account for the cognitive deficits observed in bipolar patients. This has important clinical implications as some cognitive deficits can be avoided by being judicious about the use of medications. Use of benzodiazepines and anticholinergics should be best avoided, where possible.

The wide variety of findings from generalised to specific cognitive deficits in euthymic patients of bipolar disorder may arise owing to several factors, such as patient selection and medication use. In the current study we ensured that our patients were in complete remission and their scores on YMRS and HRSD were not different from the controls and were below threshold for mood related states. A recent review (Tsitsipa et al., 2015) concluded that the neurocognitive deficit in bipolar disorder encompasses almost all neurocognitive domains. However, they suggested that only executive function and verbal memory deficit may be core deficits while other impairments probably reflect the heterogeneous nature of the subjects in various studies including symptomatology, the type and severity of Bipolar Disorder, medication status etc. We used stringent criteria for the diagnosis of Bipolar with at least 2 or more episodes of mania in the last 5 years, as evidenced by their clinical records. This ensured the validity and stability of the diagnosis. The diagnosis was made by an experienced psychiatrist (a Professor of Psychiatry) and further substantiated by using a semi-structured interview pro forma. The patients had to be in remission for at least 1 month to qualify to be in a euthymic phase.

The group which had a relatively less severe course had similar cognitive performance to the group with the more severe course. Our findings are supported by Ferrier et al (1999) who also found no difference between the good and poor outcome patients, using similar criteria as in our study. These findings lend support to the hypothesis that the specific cognitive

deficits observed in the euthymic period may actually be a trait marker of bipolar disorder, which do not necessarily worsen with worsening clinical outcome. Our findings are in accordance with recent meta-analyses (Bora et al., 2015; Bora et al., 2017) which have suggested that neurocognitive deficits are evident in first-episode bipolar patients and don't progressively worsen in most patients. A recent meta-analysis (Bortolato et al., 2015) suggested that a subgroup of individuals with bipolar disorder may even have significant impairment that even predate the onset of bipolar disorder suggesting the role of neurodevelopmental factors in bipolar disorder. However, the other hypothesis that cognitive functions worsen with illness progression (Robinson et al., 2006; Cardoso et al., 2015) cannot be completely ruled out as yet.

It has been demonstrated that cognitive deficits are a vulnerability factor for affective illness in a community sample of adolescents (Owens et al 2012). It is possible that cognitive deficits may be present before the illness onset and interact with other vulnerability factors to cause illness. This can only be studied in longitudinal studies where a high-risk cohort group is recruited before the onset of illness.

Strengths

The main strength of our study is the stringent definition of euthymia and no difference in HDRS and YMRS scores between the patients and controls. The control group had no family or personal psychiatric history.

Limitations

The diagnosis in all cases was made by an experienced psychiatrist (a Professor of Psychiatry) but a structured diagnostic tool was not used. Our sample size was small and a majority of our patients were on medication, hence the confounding effect of medication cannot be completely ruled out. We tried to address this by doing post hoc analyses, but due to the small sample size, results need to be interpreted with caution. Another limitation of our study is that the sample consisted of 90% males. Though this reflects the pattern of attendance for patients with biplolar disorders in the period when the study was conducted, this limits the generalizability of the study.

CONCLUSION

Our study demonstrates that specific executive function deficits exist in patients in the euthymic phase of bipolar disorder. These deficits can cause significant impairment in daily life of individuals with BPAD. Therefore, there is a need to develop rehabilitative and treatment models aimed at addressing/improving these cognitive deficits to achieve better functioning on recovery.

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Table 1: Comparisons of socio-demographic characteristics, mood level vocabulary test and MMSE score of the patient and control groups.

Variables	**Patients** (Mean ± SD) (N=30)	**Controls** (Mean ± SD) (N=30)	**'t'**	**'x'**	**'p'**
Age in years	34.27±8.29	34.63±8.08	1.70		0.865
Sex - N(%)					
Male	27(90%)	26(86.67%)		0.16	0.69
Female	3(10.0%)	4(13.33%)			
Mean years of education	10.27±2.80	10.40±2.87	0.178		.860
Young Mania Rating Scale(YMRS)	0.90±1.06	0.94±1.03	0.148		.883
Hamilton Rating Scale for Depression (HRSD)	1.97±1.81	1.83±1.95	0.288		.774
Vocabulary test	19.67±8.27	18.63±8.03	0.494		.623
Mini Mental State Examination (MMSE)	27.53±1.53	28.23±1.65	1.70		0.447

Table 2: Comparison of neuropsychological functions between the control and BPAD patient groups.

Neuropsychological Variables	**Patients** (Mean+SD) (N=30)	**Control** (Mean+SD) (N=30)	**t** values	**p values**	***d***	**95% CI**
Digits Forward	5.13±1.25	6.07±0.94	3.26	**.002**	0.865	-1.51 to -0.368
Digits Backward	3.30±0.79	4.07±0.78	3.76	**.001**	0.998	-1.17 to -0.364
Digit Symbol	27.00±7.31	34.33±9.25	3.41	**.001**	0.879	-11.6 to -3.02
%Perseverative Response	39.67±13.81	26.93±18.69	3.00	**.004**	0.775	4.25 to 21.2
%Perseverative Error	33.47±10.27	22.77±13.87	3.40	**.001**	0.877	4.39 to 17.0
% Non-Perseverative Errors	17.13±8.63	13.10±6.33	2.06	.043	0.532	0.119 to 7.94
%Conceptual Level Response	35.33±12.35	53.07±21.27	3.95	**.001**	1.02	-26.7 to -8.75
No. of categories completed	2.83±1.53	4.57±1.72	4.13	**.001**	1.07	-2.58 to -0.899

d=Cohen d (difference in mean divided by common standard deviation); CI= Confidence interval ; bold p values indicate significant after Bonferroni correction.

Table 3: Break-Up of Patient Meds A (n=13) and Patients Meds B (n=17) group of patients based on their medication status.

	Number of patients	**Duration of current treatment in months** (mean±SD)	**Medications**
Patient Meds A	4	19.38±10.98	Lithium alone
	2	18.24±6.02	Lithium with benzodiazepine
	3	9.48±3.08	Valproate with benzodiazepine
	2	10.38±3.02	Carbamazepine with benzodiazepine
	1	9.84	Chlorpromazine with Clozapine and Trihexyphenidyl
	1	10.38	Valproate with Carbamazepine and lorazepam
Patient Meds B	4	10.48±8.54	Carbamazepine alone
	3	19.08±6.08	Valproate alone
	3	12.05±6.82	Valproate with Atypical Antipsychotics
	2	15.02±5.33	Carbamazepine with Atypical Antipsychotics
	5	2.4±2.07	Drug free

Table 4: Summary results of the control, on medications likely to affect cognition (Patient Meds A) and on medications unlikely to affect cognition and those without medication (Patient Meds B) patient groups (divided on basis of medication status) on neuropsychological functions.

Neuropsychological Variables	**Control** (Mean±SD) (N=30)	**Group 1** (N=13)	**Group 2** (N=17)	**F values**	**p values**	***Group comparisons***
Digits Forward	6.07±0.94	4.54±0.88	5.59±1.33	9.57	**.001**	MA <C & MB; MB=C
Digits Backward	4.07±0.78	3.00±0.41	3.53±0.94	9.24	**.001**	MA<C; MB~<C; MB= M
Digit Symbol	34.33±9.25	21.31±4.97	31.53±5.63	13.48	**.001**	MA <C & MB; MB=C
%Perseverative Response	26.93±18.69	39.38+16.39	39.88±12.00	4.31	.018	
%Perseverative Error	22.77±13.87	33.38±11.86	33.53±9.26	5.66	**.006**	MB & MA<C; MB=M
% Non-Perseverative Errors	13.10±6.33	16.62±9.87	17.53±7.84	2.05	.139	
%Conceptual Level Response	53.07±21.27	34.08±14.43	36.29±10.84	7.60	**.001**	MB & MA<C; MB=MA
No. of categories completed	4.57±1.72	2.77±1.83	2.88±1.32	8.12	**.001**	M**F** & MA<C; MB=M

MA= Patient Meds A group; MB= Patient Meds B group; C= Control group; bold p values indicate significant after Bonferroni correction; ~ marginal significance indicated between MF and C on the digit backward test. Group comparisons reported are the significant differences observed between the groups following post hoc tests.

Table 5: Comparison of performance on neuropsychological test measures between less severe and more severe course BPAD patients.

Neuropsychological Variables	Less severe course patients (Mean±SD) (N=15)	More severe course patients (Mean±SD) (N=15)	t values	p values	*d*	95% CI
Digits Forward	5.13±1.36	5.13±1.19	0.000	1.00	0. 000	-0.660 to 0.660
Digits Backward	3.30±0.722	3.27±0.881	0.102	.919	0.037	-0.385 to 0.445
Digit Symbol	28.5±6.36	25.5±8.10	1.10	.278	0.404	-0.824 to 6.704
%Perseverative Response	51.9±8.75	48.4±13.3	0.851	0.402	0.314	-2.28 to 9.34
%Perseverative Error	41.00±13.83	38.3±14.14	0.529	0.601	0.191	-4.56 to 9.90
% Non-Perseverative Errors	34.7±10.0	32.27±10.73	0.642	0.526	0.231	-2.96 to 7.76
%Conceptual Level Response	34.5±10.5	36.13±14.29	0.356	0.724	-0.127	-8.08 to 4.88
No. of categories completed	2.53±1.25	3.13±1.77	1.075	0.29	-0.391	-1.39 to 0.19

d=Cohen d (difference in mean divided by common standard deviation); CI= Confidence interval