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RESEARCH ARTICLE

ACUTE AND TRANSIENT PSYCHOTIC DISORDER-ARE WORKING MEMORY DEFICITS ENDOPHENOTYPES?

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ABSTRACT

Background: Lot of research has focused on working memory (WM) deficits as trait markers and endo phenotypes in schizophrenia. Acute and transient psychotic disorders (ATPD) have on the other hand been traditionally viewed as completely remitting good prognosis psychosis and very little research has focused on whether cognitive deficits similar to schizophrenia are present in such patients. No study is available on WM in such patients in remission or on their relatives.

Aims and objectives: The current study aims at mapping working memory deficits in patients of acute and transient psychotic disorders in clinical remission and their non affected first degree relatives. This will help to determine if cognitive deficits exist in ATPD and if they are underlying genetic markers and endo phenotypes for ATPD

Methods: The study is of prospective cross sectional design carried out on a sample of 17 of which 6 were patients and 11 were first degree relatives. The measures of Working memory were Visual and Verbal N back memory, and Rey's Complex Figure Test with exposure & copy and immediate & delayed recall

Statistical Analysis: Kruskall-Wallis test was used to find the difference between performance of the patients and relatives with the normative data. Significant difference was found between the sample performance and the normative data on Visual 1 back hit (0.04) and error (0.01), Verbal 1 back hit (0.02) and error (0.00) and Rey- Osterrith Figure exposure and copy (0.00). However, no difference was found between the performance of patients and their relatives

Results: Patients of ATPD show significant deficits in working memory even when symptoms have completely remitted as do their asymptomatic first degree relatives.

Conclusions: Working memory deficits may be considered to be endo phenotypes in ATPD.

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INTRODUCTION

It has been noted from very early on that some psychotic disorders could not be categorized as either schizophrenia or affective disorders. Studies conducted by the World Health Organization (WHO), such as the International Pilot Study of Schizophrenia in 1973, yielded further evidence for the nonhomogeneity of nonorganic and non- affective psychotic disorders. (Sartorius *et al.*, 1972) The efforts to identify such "atypical schizophrenic" psychotic disorders led to the creation of the category of acute and transient psychotic disorder (ATPD) by the WHO (F.23 of ICD-10) (World Health Organization, 1993)

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This category includes a group of conditions characterized by acute onset and short duration of psychotic symptoms which do not fulfill the criteria requirements of either schizophrenia or bipolar disorder. The relationship to schizophrenia and mood disorders is not very clear with significant familial clustering being seen in both conditions. (Kendler and Diehl, 1995) It has been suggested that people with a lower cognitive reserve tend to have psychosis like experience more readily compared to those with a greater cognitive reserve. (Krabbendam *et al.*, 2005) A large body of research has focused on cognitive deficits specifically working memory deficits as trait markers and endo phenotypes in schizophrenia and to a lesser extent in bipolar probands. (Kendler and Diehl, 1995; Krabbendam *et al.*, 2005; Goldman-Rakic, 2001)

There is hardly any published literature available on cognitive deficits in ATPD. One recent study (Zanelli *et al*., 2010) in the UK has compared cognitive deficits in all psychotic disorders: schizophrenia, bipolar disorder or mania, depressive psychosis, and other psychotic disorders, which include persistent delusional disorders, acute and transient psychotic disorders, other nonorganic psychotic disorders, and unspecified nonorganic psychosis. They reported that cognitive deficits are found in all psychotic disorders but are most severe and pervasive in patients with schizophrenia and least pervasive in those with bipolar disorder or mania. No studies are available in the published literature on relatives of ATPD patients.

The current study aims at mapping working memory deficits in patients of acute and transient psychotic disorders in clinical remission and their non affected first degree relatives in an attempt to find out whether these deficits are endophenotypes of ATPD.

MATERIALS AND METHODS

Sample

The study was carried out in the psychiatry inpatient unit of a tertiary referral hospital. The study is of prospective cross sectional design carried out on a sample of 17, of which 6 were patients and 11 were their first degree relatives. The sample was acquired through simple random sampling method. 6 consecutive patients were diagnosed by a psychiatrist to have acute and transient psychotic episode using ICD -10 criteria. The symptom severity was also rated at initial contact using the BPRS -18. Remission was defined as BPRS score < 30. (Overall and Gorham, 1988)

The sample further consisted of 11 first degree relatives-(parents, siblings or children) of patients diagnosed to have ATP without any preexisting or current psychiatric morbidity/neurological disorders or substance dependence. The selected sample had to fulfill the following inclusion and exclusion criteria.

Inclusion criteria

- Patients with acute transient psychosis in remission (BPRS-18<30)
- Patients educated at least till class 10
- Patients 18-50 years of age
- First degree relatives (parents, siblings, children) of the patients with ATP
- First degree relatives 18-50 years of age
- First Degree relatives educated at least till class 10

Exclusion Criteria

- Patients with comorbid substance dependence
- Patients with history of/current neurological illnesses
- Patients with sensory deficits
- First degree relatives with substance dependence
- First degree relatives with history of/current neurological deficits
- First degree relatives with sensory deficits
- First degree relatives with history of previous or currently existing psychiatric illness as screened out by MINI- screen.
- Patients, first degree relatives, and controls not willing to give consent

Institutional Ethics Committee clearance was obtained for the study protocol and informed consent was collected from the participants.

All the patients were on atypical antipsychotics like olanzepine or risperidone at the time of evaluation. Injectable Haloperidol was given only during the hospital stay in some of the patients to control acute agitation.

Tools and Procedure

The Mini International Neuropsychiatric Interview Schedule (MINI)-Malayalam version was used for screening for psychiatric disorders in first degree relatives.

Mini International Neuropsychiatric Interview Schedule (MINI) **:** Is a widely used structured diagnostic interview developed by Sheehan and Lecrubier (Sheehan *et al*., 1998) which is highly sensitive, specific, compatible with international diagnostic criteria, and useful in clinical and research setting(Kumar *et al*., 2010).

Working memory tests: Three types of working memory were assessed – verbal working memory, visual working memory, and spatial working memory. Visual working memory was assessed using Visual N back Test, verbal working memory using Verbal N back Test, and spatial working memory was assessed using Rey Complex Figure Test. The term working memory refers to a brain system that provides short term temporary storage and manipulation of the information necessary for such complex cognitive tasks as language comprehension, learning, and reasoning; and requires the simultaneous storage and processing of information (Baddeley, 1986)

Verbal N Back Test**:** Here, thirty randomly ordered consonants are presented auditorily at the rate of one per second. Nine of the 30 consonants are repeated. The consonants which are repeated are randomly chosen. In the 1 back test the patient responds whenever a consonant is repeated consecutively. In the 2 back test the patient responds whenever a consonant is repeated after an intervening consonant. The number of hits and errors form the score in each test.

Visual N Back Test: Thirty six cards which have a randomly placed one black dot along a circle imagined to be on the card is presented. The dimension and location of the imaginary circle on each card remains constant in all cards. The patient is told to respond whenever the location of the dot repeated itself. In the 1 back test the patient is told to respond when the location of the dots consecutively repeated, and in the 2 back test the patient was told to respond whenever the location of the dot was repeated after one intervening card. The number of hits and errors form the score in each test

Rey's Complex Figure: To assess visuospatial working memory, an 8.5 inch by 11 inch card consisting of Rey's Complex Figure is used, where the patient has to copy the figure on the paper by drawing it freehand. After 3 minutes immediate recall for the figure is tested and once again after 30 minutes has lapsed for the delayed recall. On immediate recall and delayed recall trials, a score of 0,0.5, 1, or 2 is assigned to each unit of the figure based on the accuracy and placement criteria. The scores of the sample (patient and first degree relatives) were compared with normative data to determine the presence of deficits.

Statistical analysis: The data was analyzed using SPSS version 20. Pearson Chi-square was used to find the difference in the performance between the patients and their unaffected first degree relatives. Kruskall-Wallis Test was used to determine the difference in the performance of patients and their first degree relatives from the population based normative data.

RESULTS

The differences in performance on cognitive tasks were assessed between that of the probands and their first degree relatives. No difference in performance was observed between the group suggesting that both the groups have similar kind of cognitive abilities. The result of the same is shown in Table 1.

Table 1. Means, percentages and p value of patients and first degree relatives

Working	Patents n=6		Relatves n=11		P values
Memory Tasks	n	percentages	n	percentages	
Visual 1 back hit		16.7	3	27.3	0.62
Visual 1 back		0.00	2	18.2	0.26
error					
Visual 2 back hit		66.7	6	54.5	0.62
Visual 2 back		50.0	8	72.7	0.34
error					
Verbal 1 back hit		16.7	2	18.2	0.93
Verbal 1 back		0.00	2	18.2	0.26
error					
Verbal 2 back hit		50.0	4	36.4	0.58
Verbal 2 back		16.7	4	36.4	0.39
error					
Rey's Figure		0.00	0	0.00	---
Copy					
Rey's Figure		83.3	6	54.5	0.23
Immediate					
Recall					
Rey's Figure		66.7	7	63.6	0.91
Delayed Recall					

P<0.05

In the Verbal and Visual N back Tests, the relatives performed poorer than the patients. On the scores of hit (27.3%) and error (18.2%) of Visual 1 Back Test, scores of error (72.7%) on Visual 2 Back Test, scores of 1 hits (18.2%) of Verbal 1 back test, and scores of error (36.4%) of Verbal 2 Back Test, the percentage of relatives who showed deficits are higher than the patient group. Interestingly enough, percentage of patients who had deficits in visuospatial working memory was more when compared to their relatives. On the immediate recall task of the Rey's Figure, 83.3% of patients performed poorly than their relatives (54.5%). Similarly, on the delayed recall task, 66.7% of the patients put in a poor performance when compared to their relatives (63.6%). Both the patients and relatives, however, showed no difference of performance in the copying of the figure.

The difference of the performance in working memory tests by patients and their unaffected relatives from the population based normative values were also computed so as to find the variation of the former from the latter and also to confirm the presence of deficits as compared with the normative data. (Table 2)

A significant was observed in the performance of patients and relatives on Visual 1 back test when compared with the normative data. P value on the Hit score is 0.04 with patients showing more deficits than their relatives and normative values (6.83). On the Error score, the performance of relatives showed more deficits than the patients and normative values (6.91), where a significant difference was noted, with p value being 0.01.

Similarly in Verbal 1 back task, on the scores of Hit, a significant difference was obtained on the patient and relative performance when compared with that of normative data (0.02). The mean difference was high for the performance of

the patients (8.50). Contrary to this on the scores of Errors, the mean difference was high for the performance of the relatives (1.45) implying that the deficits were more in this group than that of the patients. P value was significant at 0.00.

Cognitive deficits in ATPD have scarcely been investigated, though in major psychosis like schizophrenia they have been found to be important forerunners to psychosis (Kolb, Wihshaw, 1983; Goldberg *et al.*,1993).

Table 2. Means, Standard deviation and p values of patients and relatives with respect to normative data

	Patients		Relatives		Normative Values		P value
Working Memory Measures	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Visual 1 back hits	6	6.83 (3.4)	11	6.73 (3.34)	17	6.12 (0.78)	0.04*
Visual 1 back error	6	3.67 (2.65)	11	6.91 (4.34)	17	7.65 (2.29)	0.01**
Visual 2 back hit	6	3.50 (2.07)	11	3 (1.94)	17	3.82 (0.72)	0.47
Visual 2 back error	6	12.83 (3.97)	11	15.45 (4.80)	17	13.41 (3.65)	0.18
Verbal 1 back hit	6	8.50 (1.22)	11	8.09 (0.94)	17	7.53 (0.87)	0.02*
Verbal 1 back error	6	0.67 (1.21)	11	1.45 (2.16)	17	3.82 (0.88)	0.00**
Verbal 2 back hit	6	5.67 (2.06)	11	5.73 (1.10)	17	5.12 (1.36)	0.46
Verbal 2 back error	6	4.17 (2.31)	11	5.55 (2.91)	17	6.00 (2.55)	0.32
Rey Figure Copy	6	62.58 (12.39)	11	54.5 (13.60)	17	32.64 (3.23)	0.00**
Rey Figure immediate recall	6	13.25 (18.11)	11	17.27 (15.30)	17	15.76 (4.93)	0.25
Rey Figure Delayedrecall	6	17.42 (19.49)	11	14.45 (15.76)	17	16.12 (5.15)	0.40

*p<0.05, **p<0.01

Deficits were seen more in the patients on the visuospatial task of copying the Rey Figure (62.58). P value indicates significant difference at 0.00.

DISCUSSION

ATPD according to the current understanding is viewed as a distinct disorder with a unique status. It often occurs as a stress induced or stress related disorder. There is however a diagnostic shift in some cases (Jorgensen *et al*., 1996, 1997), subsequent episodes turning out to be either bipolar disorder or schizophrenia. The occurrence of affective or schizoaffective episodes during the course of the disorder supports the reports of other authors that ATPD is still a heterogeneous category (Mojtabai 2000, Marneros *et al*., 2003; Suda, Hayashi, Hiraga, 2005).

That cognitive deficits could be a genetic trait marker in ATPD has perhaps been never considered seriously. The current study however, points to that very direction. All the three modalities of working memory namely, verbal, visual and visuospatial - are implicated in line with what is seen in schizophrenia (Park and Holzman, 1992; Keefe et al. 1995; Servan-Schreiber, 1996; Gold et al., 1997; Keefe, 2000) and affective disorders (Torrent *et al*, 2006; Gruber *et al*. 2010; Palsson *et al*. 2013). In many instances more deficits are noted in the unaffected relatives than the patients, and there is a clear leaning away from the normative values where the performance of patients and relatives on the chosen working memory tasks are concerned. As seen in the cognitive profiling of schizophrenia and affective disorders in the patients and their relatives, the differences are more in the extent and degree of impairments, rather than having any real qualitative differences (Zihl and Brunnauer, 1998). In the

background of this observation, from the results, it is logical to assume that ATP is the minor reversible variant of psychosis which has the potential to change to schizophrenia or bipolar affective disorder.

In profiling of working memory endophenotypes in schizophrenia (Tuulio *et al*., 2003; Hambrecht *et al*., 2002) and bipolar disorder (Glahn *et al*., 2008; Thermenos *et al*., 2010; Glahn *et al*., 2010), visual memory deficits in the unaffected relatives have been chronicled. However there is no literature to support or oppose the current findings that both verbal and visual working memory are impaired in the patients with ATPD and their unaffected relatives. Interestingly enough, in the performance of the task of spatial working memory, it was not the working memory that was impaired but the constrictive ability ie., visuospatial perception. This can be explained by the observation (Mervis, Robinson, and Pani, 1999) that there is an association between tests of visualization and visuospatial construction. But this does not explain why spatial working memory was not affected contrary to the expectations. Right now what can be deduced is that the poor constructive ability is an index of overall poor cognitive abilities, and the association seen in this study points to the general cognitive decline in both the probands and their unaffected relatives.

Though visuospatial working memory impairments have emerged as a cognitive endophenotypes in many studies carried out in schizophrenia and schizophrenia-spectrum disorders (Roitman *et al*., 2000; Mitropoulov, 2005), there have also been instances where this finding was not replicated (Mitropoulov *et al*., 2002). The absence of a significant association of spatial working memory deficits in the patients and their relatives is in no way conclusive unless more studies in a larger sample are carried out.

Based on the results from this study one could draw the following inferences-

1. Cognitive (Working memory) deficits are forerunners to the development of psychosis; the severity varying from ATPD to bipolar disorder to schizophrenia probably depending on other factors which still need elucidation. In other words, the vulnerability to psychosis irrespective of diagnostic category is genetically determined and cognitive deficits are the endophenotypic expression of this vulnerability. This could explain the familial clustering of schizophrenia and bipolar disorders in ATPD. The factors which determine the particular symptom cluster that is expressed are not very clear yet.
2. ATPD is a 'minor' form of Schizophrenia. In this case it would be interesting to compare the deficits in ATPD with those in schizophrenia.
3. ATPD could be actually a prodromal condition heralding the onset of more serious disorders.

In certain instances, the performance of relatives on tests were worse than the patients. Perhaps this could be attributed to the corrective effect of antipsychotic drugs. Though this is too premature a hypothesis at this point of time, if proven correct, it could have implications for early diagnosis and pharmacological prevention.

Further studies in this line could probably throw more light on the relation of psychotic disorders to each other. There are many limitations to the current study of course. Results that are of more generalizable in nature could have obtained had the sample size been larger. Owing to a small sample size, the interactions and effects of age, gender and education on the cognitive performance could not be verified. The other limitations of the study is that patients were assessed soon after their first hospital admission (because diagnostic changes may occur over time) and no patients were drug naive at the time of assessment. It would also be a worthwhile exercise to compare the cognitive functions in ATPD with schizophrenia and bipolar disorder

Conclusion

Working memory emerges in this study as a definite endophenotype of ATPD, thus placing it in a continuum of major psychiatric disorders. Whether ATPD is a precursor, a prodrome or a minor variant of major psychiatric disorders is an open question warranting further studies of similar nature with larger samples.

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