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Predicting the Outcome of First Episode Psychosis Subjects by Assessing Dorsolateral Prefrontal Cortex Volume

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Keywords

Psychotic disorders; dorsolateral prefrontal cortex; neurologic manifestations

Abstract

Aim: Dorsolateral prefrontal cortex (DLPFC), Neurological Soft Signs (NSS) and Cognitive impairment have been described as predictors of outcome of First Episode Psychosis (FEP), therefore we aimed to find the predictors of clinical, social and functional outcome variables in a cohort of first episode non affective psychotic subjects. **Subjects and Methods:** A prospective follow up study was conducted from August 2018 to August 2020 in a tertiary care hospital of South India. A semi-structured questionnaire was given to all subjects for socio-demographic details. All subjects were assessed with Heidelberg scale, Bender Gestalt Test (BGT) and underwent MRI Brain 3D volumetric scan to examine NSS, cognitive impairment, and DLPFC volume at baseline respectively. Brief Psychiatric Rating Scale (BPRS) and Social and Occupational Functioning Assessment Scale scales (SOFAS) were administered at baseline, 1 month and at three month follow up. At 3 months, clinical and socio-functional outcome was defined by BPRS scores and SOFAS scores. Pearson's correlation was found between DLPFC volume of all subjects, BPRS, BGT scores at baseline with BPRS and SOFAS at 3 months. To test the statistical significance of the comparison of mean values of all continuous clinical and demographic parameters between two groups of BPRS and SOFAS, Mann Whitney U test was used. **Results:** Smaller DLPFC volume predicted clinical, socio-functional outcome significantly. A significant moderate correlation was found between NSS and BPRS scores at baseline. **Conclusion:** Baseline right DLPFC volume can be an important predictor of clinical and socio-functional outcome in FEP.

Introduction

A disorder which had many known cultural variants included in ICD 10 in 1992 is Acute and transient psychotic disorder which subsumes the frightening experience a substantial number of people have of the first episode of acute psychosis.

Non-specific predictors such as female sex, being married, shorter duration of untreated psychosis, acute onset with presence of well-defined precipitating factors, well-adjusted pre-morbid personality traits, being in developing countries; have been described to be associated with a favourable outcome [1]. Reduced grey matter volumes are commonly observed in FEP and in prodromal states of Schizophrenia, and are vital to investigate

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for trajectory of the disorder. NSS are 'soft' neurological markers of dysfunction in domains of motor sequencing and coordination and sensory integration. Both NSS and cognitive dysfunction have also been studied in correlation with grey matter volumes in schizophrenia, however studies show inconsistent and often, contrasting results [2]. The reasons for this inconsistency could be that in most studies, baseline assessments are done in first episode patients on antipsychotic treatment, which can affect brain structure and function. Therefore, there still exists a need to dive deeper into the research to solve the dilemma regarding the possible predictors of acute psychosis.

Primary objective was assessing baseline volumetric changes in first episode non affective psychosis subjects to predict their clinical, social and functional outcome. Secondary objectives were to correlate neurological soft signs in first episode non affective psychosis subjects with their clinical, social and functional outcome. To correlate cognitive impairment in first episode non affective psychosis subjects with their clinical, social and functional outcome.

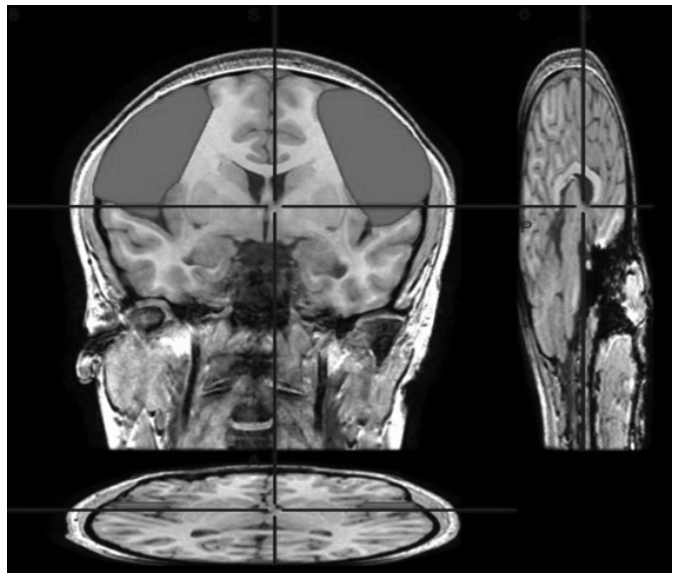

Figure 1. Manual tracing of ten subsequent anterior slices with DLPFC as region of interest using MRI-cro software

Subjects and Methods

This prospective follow up study was conducted from August 2018 to August 2020 in a tertiary care hospital of South India. As per the norms, Ethical clearance was obtained from the Ethical Committee before conducting the study. This study was conducted after obtaining the approval of the ethical committee and their guidelines were followed throughout. Subjects admitted under the department of psychiatry, diagnosed with Acute and Transient Psychotic Disorder by a consultant psychiatrist as per the ICD - 10 criteria, were enrolled by convenience sampling method. Written informed consent was taken from the subject after explaining the details of the study. Subjects with any neurological or psychiatry co-morbidity were excluded. All the subjects recruited in this study were anti-psychotic naïve. Based on the results of correlation between baseline DLPFC and the outcome variable (r = - 0.53) among first episode non affective psychosis observed in an earlier publication[2] and with 80 % power and 95 % confidence, the minimum sample size calculated was 25.

Inclusion criteria: anti-psychotic naïve and without psychiatry co-morbidity. Exclusion criteria: Subjects who did not complete any of the baseline tests were excluded.

Socio demographic details were recorded using the semi-structured questionnaire specifically designed for this study. Clinical variables including Medical co-morbidity or presence of associated stress were also noted. Mini International Neuropsychiatric Interview version 5 (MINI) was administered to confirm the diagnosis as well as to rule out other major psychiatric disorders. Psychopathology was assessed using Brief Psychiatry Rating Scale (BPRS) and Heidelberg scale was administered to assess the neurological soft signs. Cognitive Deficits were assessed using Bender Gestalt Test (BGT). In all these subjects, MRI Brain Plain volumetric 3-D scan was done. MRIcro software, freely available online, was installed and used to map out the boundaries of Dorsolateral prefrontal cortex (DLPFC) on these images and to calculate its volume bilaterally. Morphometric analysis of the DLPFC was done using the Region of Interest (ROI) analysis on the available MRI scans. Morphometric measurements were conducted blind to the clinical data using MRIcro software. It is available in the public domain and can be downloaded from the internet (http://www.sph.sc.edu/comd/rorden/mrizip.zip).

Scanning protocol

T1- weighted three-dimensional Magnetization- Prepared Rapid Acquisition Gradient Echo Imaging was performed in the sagittal and coronal plane (TR = 8.47 ms, TE = 3.25 ms, FOV = 100.00, slice thickness = 1.00, matrix = 0/0/0 scan time = 14 minutes 3 seconds). A set of 180 images covering the entire brain was obtained.

The most posterior part of the genu was located and used as the first slice in measuring DLPFC. The boundaries of the DLPFC were then manually outlined as per the following anatomical relations:

- Superior boundary: Superior frontal sulcus
- Inferior boundary: Posterior lateral fissure and horizontal ramus of the anterior lateral fissure
- Lateral border: Edge of the cerebral cortex

– Medial border: Created by connecting the deepest points on the superior frontal sulcus and the lateral fissure

Ten subsequent anterior slices were traced as depicted in the picture and the volume automatically calculated as number of pixels by the MRI-cro software. The same procedure was repeated for both the right and left DLPFC (Figure 1).

Follow-up assessments

Clinical outcome was based on BPRS scores at 3 months. At 1 and 3 months follow up, clinical and social and occupational-functional outcome was assessed by BPRS and SOFAS and scores were recorded. After obtaining the scores, subjects were divided into two groups as good responders or poor responders based on whether they had fall in BPRS scores over 3 months greater than 50 % or lesser than 50 % respectively [3] Similarly, subjects were divided into good or poor functional outcome groups based on whether at 3 months follow-up they had SOFAS score more than or less than 60 respectively [4].

Statistical analysis

Statistical analysis was done using IBM SPSS version 20.0 software. The results are expressed in Median (IQR) for continuous variables and in frequency (percentage) for categorical variables. Pearson's chi-square test with Fisher's exact test was applied to find the association between socio-demographic categorical variables, like sex, education, monthly income, occupation, marital status, type of family, f/h/o psychiatric disorder/ suicide attempt/ mood disorder/psychotic disorder, of all subjects with BPRS at 3 months. Pearson's correlation was found between DLPFC volume of all subjects, BPRS, BGT scores at baseline with BPRS and SOFAS at 3 months and its significance was tested using linear regression t-test. To test the statistical significance of the comparison of mean values of all continuous clinical and demographic parameters between two groups of BPRS and SOFA, Mann Whitney U test was used. A p value < 0.05 was considered to be statistically significant.

Results

Frequency distribution of socio-demographic variables among the two groups. In our study, subjects recruited were assessed at baseline, at 1 month and at 3 months. At 3 months, 22 subjects were divided into two groups based on clinical and socio-occupational and

Table 1. Frequency distribution of socio-demographic variables among the two groups of subjects based on change in Brief Psychiatric Rating Scale (BPRS) scores over three months.

		Good responders (Fall in BPRS scores over 3 months greater than 50 %) (n = 17)	Poor responders (Fall in BPRS scores over 3 months lesser than 50 %) (n = 5)	p value	Total subjects (n = 22)
Socio-demographic variables		No (%)	No (%)		No (%)
Sex	Males	6 (35.3)	4 (80)	0.135	10 (45.5)
	Females	11 (64.70)	1 (20)		12 (54.5)
Highest educational qualification	Primary	1 (5.9)	3 (60)	-	4 (18.2)
	Secondary	6 (35.3)	0 (0)**		6 (27.3)
	12th passed	10 (58.8)	2 (40)		12 (54.5)
Occupation	Unemployed	8 (47.1)	1 (20)	0.360	9 (40.9)
	Semi professional	9 (52.9)	4 (80)		13 (59.1)
Marital status	Single	13 (76.5)	4 (80)	1.00	17 (77.3)
	Married	4 (23.5)	1 (20)		5 (22.7)
Type of family	Nuclear	16 (94.1)	5 (100)	1.00	21 (95.5)
	Third generation	1 (5.9)	0 (0)		1 (4.5)
Family monthly income	< 50K	1 (5.9)	0 (0)	1.00	1 (4.5)
	50K to 70K	10 (58.8)	4 (80)		14 (63.6)
	> 70K	6 (35.3)	1 (20)		7 (31.8)

*(p value < 0.05 is considered significant)

Table 2. Comparison of assessment variables among the two groups of subjects based on change in Brief Psychiatric Rating Scale (BPRS) scores over three months.

Variables	Good responders (Fall in BPRS scores over 3 months greater than 50 %) (n= 17)	Poor responders (Fall in BPRS scores over 3 months lesser than 50 %) (n = 5)	p value	Total subjects (n = 22)
	Median (IQR)	Median (IQR)		Median (IQR)
Dorsolateral prefrontal cortex volume (DLPFC) (cc):				
Left DLPFC volume	15.18 (5.55)	12.88 (2.92)	0.055	14.54 (4.04)
Right LDPFC volume	16.12 (4.80)	14.19 (2.95)	0.042*	15.90 (3.97)
BPRS scores				
Baseline	54 (16)	56 (9)	0.753	55 (10)
At 1 month	31 (8)	29 (3)	0.663	29 (4)
At 3 months	25 (3)	24 (4)	0.812	24.50 (3)
Neurological soft signs (NSS) scores				
Motor coordination	10 (3)	8 (4)	0.233	9 (3)
Sequential Complex Motor Performance	7 (2)	6 (1)	0.054	6 (2)
Sensory integration	10 (5)	9 (3)	0.067	9 (3)
Primitive reflexes	3 (2)	1 (2)	0.055	2 (2)
Total NSS scores	31 (11)	25 (6)	0.099	26 (8)
Bender gestalt test scores	22 (2)	22 (5)	0.491	22 (5)

*(p value < 0.05 is considered significant)

Table 3. Comparison of assessment variables among the two groups of subjects based on change in Social and Occupational Functioning Assessment Scale (SOFAS) over three months.

Variables	Good functional outcome (SOFAS > 60) n = 14	Poor functional outcome (SOFAS < 60) n = 8	p value
	Median (IQR)	Median (IQR)	
Dorsolateral prefrontal cortex volume (DLPFC)			
Left DLPFC volume	15.64 (4.89)	12.46 (0.87)	0.01*
Right DLPFC volume	16.93 (3.85)	13.42 (1.06)	0.01*
Neurological soft signs (NSS)			
Motor coordination	8 (3)	10 (1)	0.001*
Sequential complex motor performance	6 (1)	7 (2)	0.001*
Sensory integration	9 (1)	13 (5)	0.001*
Primitive reflexes	1 (2)	3 (3)	0.050*
Total NSS scores	23.5 (4)	32.5 (8)	0.001*
Bender gestalt test (BGT)			
BGT scores	24.5 (5)	21.50 (1)	0.067

*(p value < 0.05 is considered significant)

Table 4. Correlation between assessment variables among two groups based on change in Brief psychiatric rating scale (BPRS) scores over time.

Variables	Change in brief psychiatric rating scale (BPRS) scores over time					
	BPRS baseline		BPRS at 1 month		BPRS at 3 months	
	r	p value	r	p value	r	p value
Dorsolateral prefrontal cortex volume						
Left DLPFC volume	- 0.460	0.031*	- 0.208	0.353	- 0.171	0.448
Right DLPFC volume	- 0.506	0.016*	- 0.239	0.285	- 0.205	0.359
Neurological soft signs (NSS)						
Motor coordination	0.676	0.01*	0.223	0.319	0.096	0.672
Sequential complex motor performance	0.563	0.06	0.493	0.020*	0.334	0.128
Sensory integration	0.523	0.012*	0.282	0.204	0.08	0.69
Primitive reflexes	0.483	0.023*	0.52	0.012*	0.20	0.36
Total NSS scores	0.64	0.01*	0.39	0.07	0.17	0.44
Bender gestalt test (BGT)						
BGT scores	- 0.8	0.20	- 0.02	0.91	- 0.18	0.40

*(p value < 0.05 is considered significant)

functional outcome. Fall in BPRS scores over 3 months greater than 50 % and fall in BPRS scores over 3 months lesser than 50 % were defined as good responders and poor responders respectively. Similarly, good and poor functional outcomes were defined by SOFAS scores greater or lesser than 60 at 3 months respectively.

In our study, mean of age of all the subjects included was 25.00 ± 11.48. Mean age of good responders and poor responders were 25.35 ± 10.7 and 25.20 ± 15.32 respectively which when compared was not statistically significant (p = 0.43). Median of DUP among good responders and poor responders were 9 (20) and 14 (16) respectively. The comparison was not statistically significant (p = 0.578). Among good responders, 4 (80 %) and 1 (20 %) subjects were with and without associated stress respectively which was not statistically significant. Among poor responders, 11 (64.7 %) and 6 (35.3 %) subjects were with and without associated stress respectively (p = 1.000) (Table 1).

Median of Left DLPFC volume and Right DLPFC volume of all subjects were 14.54 (4.04) and 15.90 (3.97) respectively. Among good responders and poor responders, median of Left DLPFC volumes (cc) were 15.18 (5.55) and 12.88 (2.92) respectively. The comparison was not found to be statistically significant (p = 0.055). Among the good and poor responders, median of Right DLPFC volume volumes (cc) were 16.12 (4.80) and 14.19 (2.95) respectively. The comparison was found to be statistically significant (p = 0.042). In our study, median comparison of NSS scores and BGT scores among two groups based on change in BPRS scores over 3 months were not statistically significant (Table 2). Comparing median of left and right DLPFC volume among two groups based on change in SOFAS scores over 3 months revealed significant difference. Statistically significant negative correlation was found between Left DLPFC volume, Right DLPFC volume and BPRS scores at baseline (Table 3). Statistically significant positive correlation was found between left DLPFC volume and SOFAS scores at baseline (Table 4).

Discussion

In our study of 22 subjects, we found that at three months follow-up five subjects had poor clinical outcome while eight subjects had poor socio-occupational functional outcome. In our study, the mean of age of subjects who had good clinical outcome was higher than those who had poor clinical outcome but the difference was not statistically significant. A two year follow up study by Laura and associates revealed that FEP in younger age group had worse clinical outcomes [5]. Our study could not replicate similar results which might be due to small sample size.

There were ten males and twelve females depicting higher incidence of acute psychosis in females whereas Preston and associates revealed higher preponderance

and worse outcomes in males [6]. Our study did not show any significant difference which might be due to a small sample size enrolled in our study. The average left DLPFC volume of good responders was higher than among poor responders. The difference though was not statistically significant ($p = 0.055$). The average right DLPFC volume of good responders was higher than average right DLPFC volume of poor responders. The difference was statistically significant ($p = 0.042$). This is in line with the notion that FEP results from an insult to the brain during pre or perinatal brain growth, resulting in maldevelopment or failure to reach normal brain structural shape and size [7]. We established a statistically significant negative correlation between left DLPFC volume and BPRS scores at baseline ($p = 0.031$). Similarly, the correlation between right DLPFC volume and BPRS scores at baseline was also found to be statistically significant ($p = 0.016$). Similarly, Zhang and associates found significant correlation between cortical grey matter volumes and total PANSS scores [8]. Furthermore, our findings support the hypothesis that grey matter volume changes in the first episode psychosis are related to the progression of the disorder, are clinically relevant in determining prognosis and they emphasize the importance of early intervention aiming to slow down or stop progressive brain volume loss [9].

Baseline average of total NSS scores among subjects who had poor clinical outcome was higher than among subjects who had good clinical outcome at 3 months though was not statistically significant. None of the average scores of subscales of NSS was found to be statistically significant although all were present in higher number in the poor responders group which is in line with the findings of a recent study [10]. The presence of soft neurological signs in patients with other psychosis supports the hypothesis that neurological abnormalities are not specific to any particular kind of psychosis [11]. We found statistically significant positive correlation between total NSS scores of all subjects with BPRS scores of all subjects at baseline. We found significant positive correlation between motor coordination scores, sensory integration scores and primitive reflexes scores of all subjects with BPRS scores of all subjects at baseline. Our findings support the evidence which advocates NSS, motor coordination in particular, as potential endophenotype for schizophrenia [12].

Average BGT scores were higher in good responders than poor responders. This finding although suggests that subjects who had performed better at baseline on BGT scale on follow-up had better clinical outcome, the difference was not statistically significant. In this study, only BGT was used to measure visual motor functioning and visual perception. Whereas, in a ten year follow-up study of epidemiological cohort, it was found that baseline memory for design poor performance was associated with a higher negative symptom score at follow-up. They used a battery of tests instead of one test as in our study which can be a suitable explanation as to why our study could not replicate their results [13]. We also established negative correlations between BGT scores of all subjects and BPRS scores of all subjects at baseline, one month and at three months but were not statistically significant. Lindgreen and associates found that subjects with higher baseline processing speed had better clinical outcome at one year follow up period. They used a variety of tests to measure cognition whereas we only used BGT test for visual motor functioning and visual perception and had smaller follow up period. Besides, the effect of antipsychotic medications on the follow up assessments was not taken into account [14].

Average left DLPFC volume of fourteen subjects with good functional outcome was higher than average DLPFC volume among eight subjects with poor functional outcome. The difference was statistically significant. Mean right DLPFC volume among subjects with good functional outcome was higher than average right DLPFC volume among subjects with poor functional outcome. The difference was statistically significant. Another study found al DLPFC volume was a significant predictor of functional outcome at 1 year which is similar to our findings [15]. Our finding supports the hypothesis that grey matter volumes in FEP are not only associated with clinical but also with functional outcome [9]. In our study, we found statistically significant positive correlation between Left DLPFC volume, right DLPFC volume and SOFAS scores at baseline ($p = 0.04$). On follow up at one and three month assessments, there was a mild positive correlation between left DLPFC volume, right DLPFC volume of all subjects and SOFAS scores of all subjects. Our findings support the hypothesis that DLPFC volumes predict the functional outcome of first episode psychotic subjects [15]. Our findings support the hypothesis that DLPFC is involved in the planning and monitoring of everyday behaviour, in regulation of response to environmental stimuli and in selection of task appropriate cognitive strategies. Lesser DLPFC volumes lead to impaired recruitment of these neuro-cognitive rate limiting functions which are vital for functional recovery [15].

In terms of results, average total NSS scores were higher among poor functional outcome group than good functional outcome group which were statistically significant. On comparison of average scores of four subscales of Heidelberg scale among the two groups at three months, we found scores in all four were higher in poor functional outcome group and the differences were statistically significant suggesting that at baseline higher neurological soft signs can predict worse socio-function-

al outcomes on follow-up. Our findings support the hypothesis that neurological soft signs are early-detectable, easily measurable, reliable predictors of functional and clinical outcome [16]. We found statistically significant negative correlation between Total NSS scores of all subjects and SOFAS scores of all subjects at baseline ($p = 0.03$) and at 3 months ($p = 0.016$). In our study, we found significant correlation between motor coordination scores of all subjects and SOFAS scores of all subjects at baseline ($p = 0.03$). We also found significant correlations between sequential complex motor performance scores, primitive reflexes of all subjects with SOFAS scores of all subjects at baseline and at 3 months. Our findings support the hypothesis that neurological soft signs, sequential complex motor performance and primitive reflexes are significant predictors of the outcome of first episode subjects [2,17].

In our study, the average BGT score among good functional outcome group was higher than among poor functional outcome group though it was not statistically significant. In our study, we found mild positive correlations between BGT scores and SOFAS scores at baseline, at one month and at three months. At all the three assessment periods, correlation was not statistically significant which could be due to small sample size and assessing only with BGT rather than tests with wide range assessments of the cognitive domains. Oomen and associates in a cluster analysis found lower clinical global functioning in the subgroup with severely impaired cognition compared to the moderately impaired cluster at baseline and 6-month follow-up. They used brief assessment of cognition in schizophrenia, to assess various domains of cognition, WHODAS, for self-reporting the global functioning and disability, and clinical global functioning was evaluated by GAF. They also found a gradual and stepwise increase in disability, with the relatively preserved cluster having lower disability scores compared to the moderately impaired and severely impaired cluster [18].

In terms of limitations, our study was conducted on only a small sample size that was followed up for short period of time. Secondly, enrolled subjects were not compared with healthy controls and standardization of the treatment given was not done. Third, only BGT was used which only measures visual motor functioning and visual perception. Other domains of cognition were not measured and taken into account.

In conclusion, baseline right DLPFC volume can be an important predictor of clinical and socio-functional outcome in FEP. Assessing NSS and visual motor functioning correlated somewhat to the outcome of FEP. Longer follow-up studies in large cohorts are needed in order to shed more light in investigating the predictors of the outcome after the onset of the illness and its clinical correlates. Future research will try to find out the implication that these results may have on the clinical evolution of the disease.

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Conflict of Interest

None to declare.

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