Dorsolateral prefrontal lobe volume and neurological soft signs as predictors of clinical social and functional outcome in schizophrenia: A longitudinal study

Rishikesh V. Behere
Department of Psychiatry, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

ABSTRACT

Schizophrenia is a disorder with variable outcome and the ability to predict the outcome has important clinical utility. Neurological soft signs (NSS) and dorsolateral prefrontal cortex volumes have been described as trait markers for schizophrenia and their relation to long-term outcome in schizophrenia has not been well studied. The aim of this study was to examine the correlation between baseline dorsolateral prefrontal lobe (DLPFL) volume and NSS scores to clinical and functional outcome variables in a cohort of schizophrenia patients who were anti-psychotic naïve at baseline. Fourteen anti-psychotic naïve schizophrenia patients whose baseline magnetic resonance imaging scans, NSS scores and positive and negative signs and symptoms scale (PANSS) scores (assessed in drug naïve state) were available were reevaluated after a mean follow-up period of 74.2±24.2 months. The clinical outcome variables measured was PANSS. The social and functional outcome was assessed comprehensively by the socio occupational functioning scale and the Strauss Carpenter outcome scale. The DLPFL volume was measured from the baseline scans using the region of interest method. Statistical analysis was done using the paired samples t-test and the Pearson’s correlation co-efficient. The results showed that smaller left DLPFL volume and greater primitive reflexes at baseline predicted greater negative symptoms and poorer functional outcome on follow-up. This study also demonstrates the clinical utility of NSS as a simple bedside tool in assessing schizophrenia patients.

Key words: Dorsolateral prefrontal lobe, primitive reflexes, schizophrenia, social and occupational functioning

INTRODUCTION

Schizophrenia has generally been considered as a chronic disorder with a progressive course and poor outcome. The earliest systematic long term follow-up of schizophrenia patients was conducted by Kraepelin who concluded that dementia praecox is a disorder with a progressive course and poor prognosis[1]. Landmark long-term follow-up studies by Bleuler[2] and Tsuang[3] have reported rates of remission of 26-43% and 50-75% patients may remain clinically stable with stable deficits. 1-4% patients are reported to have chronic deteriorating course. Similar findings have been reported from Indian studies. Thara et al.[4] in a 20 year follow-up study have reported complete remission and continuous course of 8.2% and episodic course with stable deficits in 44.3%. Recent Indian study from Vellore[5] also reported that 50% patients had residual deficits over 1 year follow-up. Hence from the clinical perspective, markers predicting outcome of schizophrenia patients at baseline is of great importance and can have important treatment implications.

Predictors of outcome
Various 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 premorbid personality traits, being in developing countries; have been described to be associated with a favorable outcome in important studies such as International Pilot Study of Schizophrenia.[6]

While clinical and demographic factors can provide important pointers to predicting outcome, neurobiological markers can potentially be predictors of outcome in schizophrenia. Neurological soft signs (NSS) and prefrontal cortex volumes have been described to be trait markers of schizophrenia, which can persist throughout the course of illness and are associated with a ‘deficit’ form of schizophrenia which has a poor outcome.[7]

NSS as predictor of outcome
NSS are ‘soft’ neurological markers of dysfunction in spheres of motor coordination, sensory integration, sequencing of complex motor acts and also includes primitive reflexes.[8] These have been consistently demonstrated in treated and antipsychotic naïve schizophrenia and have been described to be trait markers reflective of neuro-developmental etio-pathogenesis of schizophrenia.[9] NSS have been found to correlate with smaller caudate, cerebellar and dorsolateral prefrontal cortex volumes in schizophrenia.[10] In longitudinal 1-3 year follow-up studies NSS has been found to variably predict outcome.[11] Long-term prospective longitudinal studies, including multiple functional outcomes, are required to clearly understand NSS as predictors of outcome.

Neuroimaging findings as predictor of outcome
Neuroimaging studies in schizophrenia have consistently demonstrated prefrontal cortex volume, temporal lobe volume deficits in comparison to healthy controls. Milet et al. (2003)[12] in their study on 123 schizophrenia patients found that baseline temporal lobe gray matter volumes correlated with persistent auditory hallucinations on 5 year follow-up, however, brain volumes did not predict any outcome measures. vanHaren et al. (2003)[13] did not find any significant correlation between baseline gray matter volumes and outcome over a 2 year period. Prasad et al. (2005)[14] however, reported that baseline volumes of the dorsolateral prefrontal cortex predicted short term socio-occupational outcome at the end of 1 year but not at the end of the 2nd year. In a study by Cahn et al. (2006)[15] brain volumes in first year of illness was found to predict clinical and functional outcome over a period of 5 years. In a recent study Mitelman et al. (2009)[16] reported progressive loss of putamen volumes in patients with poorer outcome as compared to better outcome schizophrenia over 4 year follow-up.

The above findings suggest that though biological markers such as NSS and brain volumes have been consistently demonstrated in schizophrenia; their reliability as predictors of outcome has been inconsistent. The factors contributing to this inconsistency could be manifold. (1) In most studies baseline assessments are done in first episode patients on antipsychotic treatment. It has been demonstrated that antipsychotic treatment can affect brain structure and function and may not accurately predict outcome. (2) There is wide heterogeneity in outcome measures used in previous longitudinal studies. The above studies[11-16] have used varied outcome measures such as improvement in psychopathology scores, global assessment of functioning (GAF), strauss carpenter outcome scale (SCOS), and clinical global impression scale. In recent studies it has been demonstrated that current outcome measures do not capture real life situations and need to be multidimensional including dimensions of clinical improvement and social outcome.[17] Socio-functional outcome scales also need to be culturally sensitive as social occupational roles expected out of patients can be influenced by their cultural background.

Hence the aim of this study was to assess baseline dorsolateral prefrontal cortex volume and NSS in anti-psychotic naïve schizophrenia subjects and its correlation with clinical and socio-functional outcome as assessed by culturally sensitive scale validated for use in Indian population; on longitudinal follow-up. The hypothesis was that greater negative symptoms and poor socio-occupational functional outcome on follow-up will be associated with lower baseline dorsolateral prefrontal cortex volume and greater baseline NSS scores.

MATERIALS AND METHODS
Subjects
Study subjects were recruited from the Schizophrenia Clinic of the National Institute of Mental Health and Neurosciences, Bangalore, India. As a part of ongoing neurobiological studies on schizophrenia,[18] these patients had already been evaluated between 1999 and 2002 (when they were anti-psychotic-naïve). At baseline patients meeting Diagnostic and statistical manual of mental disorders (DSM) IV criteria of schizophrenia in age range of 18-45 years, with no previous exposure to antipsychotics were recruited and assessed independently by two qualified psychiatrists through independent clinical interview. Patients with any substance dependence in the last 6 months (except nicotine), co-morbid medical or neurological illness were excluded from the study. The baseline clinical and brain structural data were available for these patients. These patients were personally contacted through two rounds of letters, telephone calls and home visits and requested to be a part of this study. Seventeen of these patients who could be contacted and gave their consent were recruited for the study. Prior to follow-up recruitment the study subjects were again reassessed for any of the exclusion criteria as described above.
Baseline assessments
At baseline clinical and demographic details were assessed using a semi structured pro-forma. Psychopathology was assessed using the positive and negative signs and symptoms scale (PANSS)
 and NSS was assessed using the modified neurological evaluation scale.
 Magnetic resonance imaging (MRI) was done at baseline as a part of ongoing neurobiological studies during the period 1999-2002 when these patients were antipsychotic naive. MRI was done with Siemens 1.5 Tesla Mangetrom vision system (Erlangen, Germany) at the Department of Neuroimaging and Interventional Radiology, NIMHANS.

Scanning protocol
T1-weighted three-dimensional Magnetization-Prepared Rapid Acquisition Gradient Echo imaging was performed in the sagittal plane. (TR=9.7 ms, TE=4 ms, nutation angle=12°, FOV=250 mm, slice thickness 1 mm, NEX=1, matrix=200 × 256 scan time 6 min 12 s). A set of 160 images covering the entire brain was obtained.

Follow-up assessments
On follow-up clinical, demographic and treatment details were reassessed using a semi structured pro-forma. All follow-up assessments were done by the author blind to the baseline scores. Psychopathology and NSS were reassessed using the PANSS and modified neurological evaluation scale respectively. The socio-occupational functioning was assessed using two scales. (1) SCOS (2) social occupational functioning scale (SOFS). The SOFS is a scale validated to assess socio-occupational functioning in Indian schizophrenia patients with good reliability and validity. It is a 15 item scale with each item rated from 1 (no impairment) to 5 (extreme impairment) and hence a greater score on SOFS indicates a poorer socio-occupational functioning. It covers the domains of adaptive living skills, social appropriateness and interpersonal skills. Subjects were also assessed for comorbid depression with hamilton depression rating scale (HDRS) and for anti-psychotic related movement disorders using abnormal involuntary movement scale (AIMS) and Simpson Agnus extrapyramidal rating scale (SAS). Morphometric analysis of the dorsolateral prefrontal cortex was done using the Region of Interest (ROI) analysis on the available baseline MRI scans. All morphometric analysis were done by the author on coded images, blind to the status of the subjects.

ROI
Morphometric measurements were conducted blind to clinical data using MRlcor software. It is available in the public domain and can be downloaded from the internet (http://www.sph.sc.edu/comd/rorden/mrizip.zip). MRlcor allows efficient viewing and exporting of brain images and can be used to identify ROI's.

The dorsolateral prefrontal lobe (DLPFL) was measured as per the method described by Gilbert et al. All measurements were done in the coronal section at a magnification of ×3. The most posterior part of the genu was located and used as the first slice in measuring the DLPFL. The boundaries of the DLPFL 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 and the volume automatically calculated as number of pixels by the MRlcor software. The same procedure was repeated for both the right and left DLPFL.
**Statistical analysis**

The statistical analysis was performed using the Statistical Package for Social Sciences-13.0. Paired samples t-test was used to compare baseline and follow-up scores of psychopathology and NSS. Pearson’s correlation analysis was used to study correlation between DLPFL volume and scores on PANSS, NSS, SOFS and SCOS. The statistical significance was set at \( P < 0.05 \) (two-tailed).

**RESULTS**

Seventeen subjects who could be contacted and gave consent were recruited for the study. MRI images for analysis were available for 14 patients. The demographic and illness related variables are presented in Table 1. The mean duration of follow-up was 74.2±24.2 months. Patients had received antipsychotics for mean duration of 56.9±29.3 months during the course of the illness at a mean dosage of 296.1±185.2 mg/day in Chlorpromazine (CPZ) equivalents. A comparison of baseline and follow-up psychopathology and NSS scores is given in Table 2.

On follow-up, there was a significant improvement in positive syndrome and general psychopathology scores. No change was observed in negative syndrome and NSS scores. None of the patients on follow-up qualified for depressive episode on HDRS nor had any drug induced extra pyramidal syndrome or movement disorder as assessed on SAS and AIMS; hence ruling out the possibility of the patients having any secondary negative symptoms.

Correlation analysis was performed between each of the baseline predictors of NSS sub-scores and DLPFL volumes with outcome variables of SOFS, SCOS and PANSS [Table 3]:

1. Correlation between baseline NSS scores and outcome variables: There was a significant positive correlation between baseline primitive reflex score and SOFS \( r=0.68, P=0.03 \) and follow-up negative syndrome scores \( r=0.75, P=0.01 \).

2. Correlation between baseline DLPFL and outcome variables: There was a significant negative correlation between baseline DLPFL volume and SOFS \( r=-0.53, P=0.05 \) and follow-up negative syndrome scores \( r=-0.6, P=0.02 \).

**DISCUSSION**

To summarize, the main findings of this study were (1) There was a significant improvement in positive syndrome and general psychopathology scores however there was no change in negative syndrome score on follow-up. (2) There was no significant change in any of the NSS scores on follow-up. (3) Higher baseline primitive reflex score was associated with poorer socio occupational functioning and greater negative symptoms on follow-up (4) Smaller DLPFL volume at baseline was associated with poorer socio occupational functioning and greater negative symptoms on follow-up.

The finding of no change in negative syndrome on follow-up is consistent with our understanding of the psychopathology of schizophrenia, that positive symptoms are state related and respond well to antipsychotic treatment whereas negative symptoms are trait related and persist despite treatment.[26] The persistence of NSS over the course of illness and absence of any significant improvement on follow-up suggests that NSS are trait related and support the hypothesis of a neuro-developmental etio-pathogenesis of schizophrenia.[9,10]

**Table 1: Clinical and demographic characteristics of study subjects on follow-up**

| Variable                      | Mean±SD         |
|-------------------------------|-----------------|
| Age in years                  | 32.7±7.2        |
| Education in years            | 11.2±2.9        |
| Sex ratio (M:F)               | 9:8             |
| Age at onset (in years)       | 24.9±6.5        |
| Duration of untreated psychosis (in months) | 25.8±26.9 |
| Duration of illness (in months) | 100.1±37.1     |
| Duration of follow-up (in months) | 74.2±24.2 |
| Duration of exposure to antipsychotics (in months) | 56.9±29.3 |
| Mean dose of antipsychotic per day (CPZ equivalents) | 296.1±185.2 mg/day |

**Table 2: Comparison of baseline versus follow-up clinical data**

| Variables                        | Baseline assessments Mean±SD | Follow-up assessments Mean±SD | \( \rho \) | \( P \) |
|----------------------------------|-----------------------------|-------------------------------|--------|--------|
| PANSS                            |                             |                               |        |        |
| Positive syndrome                | 24.9±5.5                    | 14.1±9.4                      | 4.067  | 0.001***|
| Negative syndrome                | 18.3±8.6                    | 18.0±7.7                      | 0.085  | 0.934  |
| General psychopathology          | 38.5±8.8                    | 31.6±8.7                      | 2.298  | 0.039* |
| NSS                              |                             |                               |        |        |
| Motor co-ordination              | 2.0±2.1                     | 1.9±2.1                       | 0.083  | 0.935  |
| Sequential complex movements     | 4.4±3.1                     | 4.1±2.8                       | 0.206  | 0.841  |
| Sensory integration              | 4.3±3.4                     | 2.3±2.2                       | 1.096  | 0.299  |
| Primitive reflex                 | 2.8±2.4                     | 1.6±1.5                       | 0.182  | 0.860  |
| Total scores HAM-D               | –                           | 4.4±4.2                       | –      | –      |
| Total score SAS                  | –                           | 1.3±1.4                       | –      | –      |
| Total score AIMS                 | –                           | 1.2±1.9                       | –      | –      |
| Total score SCOS                 | –                           | 10.6±3.9                      | –      | –      |
| Total score SOFS                 | –                           | 26.9±11.8                     | –      | –      |
| Dorsolateral prefrontal–cortex left (sq pixels) | 11593.9±1273.1     | –                            | –      | –      |
| Dorsolateral prefrontal–cortex right (sq pixels) | 11416.6±1628.6   | –                            | –      | –      |

*\( P < 0.05 \); ** \( P < 0.001 \); \* Paired samples t-test; \*\* Brain volume data are available for 14 patients as 3 MRI images could not be retrieved; PANSS – Positive and negative signs and symptoms scale; NSS – Neurological soft sign; SAS – Simpson-angus scale; AIMS – Abnormal involuntary movement scale; SCOS – Strauss carpenter outcome scale; SOFS – Social occupational functioning scale; MRI – Magnetic resonance imaging; HAM-D – Hamilton depression rating scale; \( n=17 \)
NSS and outcome
Earlier studies on NSS predicting outcome in schizophrenia have shown inconsistent results. Whitty et al. (2003)\[27\] found that the primitive reflexes which were considered as ‘Harder’ signs did not improve over a 6 month follow-up as compared to the ‘softer’ signs. Frontal release signs have been demonstrated to be associated with frontal lobe dysfunction on neuropsychological tests.\[28\] Hence the presence of primitive reflexes may indicate an underlying brain structural abnormality which may in turn contribute to a poorer outcome in schizophrenia.

DLPFL volume and outcome
Based on observations of correlation between negative symptoms, frontal structural abnormalities and outcome, Staal et al. (1999)\[29\] had suggested that a relationship may exist between poor outcome and frontal lobe dysfunction. Subsequent studies have not demonstrated any consistent relationship between outcome and baseline brain volumes.\[30,31\] Greater emphasis has been laid on progressive gray matter changes and its relationship to outcome.\[30\] Smaller baseline brain volumes have been consistently demonstrated in prodromal stages, early stages of psychosis and also in unaffected first degree relatives.\[31\] Structural brain changes are being increasingly realized as potential endophenotype markers for schizophrenia.\[28\] Hence, prediction of outcome based on baseline brain volumes prior to initiation of antipsychotics is of great clinical utility. A study by Prasad et al. (2005)\[14\] showed that the Left DLPFL volume correlated with poor outcome as measured on SCOS at the end of 1 year but not at the end of 2 years, suggesting that baseline brain volumes may predict only short but not long term outcome. Our study findings are supported by results from study by Cahn et al. (2006)\[32\] in which brain volumes in first year of illness were found to predict clinical and functional outcome over a period of 5 years. Our study demonstrates the clinical utility of baseline left DLPFL volume in predicting even long term outcome. Hence smaller baseline DLPFL volumes are associated with greater magnitude and persistence of these trait deficits (negative symptoms and NSS) which can contribute to a poorer outcome in schizophrenia.

Table 3: Correlation between baseline neurological soft sign, dorsolateral prefrontal lobe volume and follow-up outcome variables (social occupational functioning scale, Strauss Carpenter outcome scale, neurological soft sign)

| Variables                  | SOFS (follow-up) | SCOS (follow-up) | Negative syndrome (follow-up) | Positive syndrome (follow-up) | General psychopathology (follow-up) |
|----------------------------|------------------|------------------|-------------------------------|-------------------------------|-----------------------------------|
|                            | \(r\) | \(P\) | \(r\) | \(P\) | \(r\) | \(P\) | \(r\) | \(P\) | \(r\) | \(P\) |
| MOTCO (baseline)           | 0.08 | 0.3 | −0.15 | 0.6 | 0.05 | 0.9 | 0.071 | 0.8 | 0.08 | 0.793 |
| SCOMP (baseline)           | 0.795 | 0.3 | −0.22 | 0.5 | −0.11 | 0.7 | 0.12 | 0.7 | −0.08 | 0.8 |
| SENINT (baseline)          | 0.248 | 0.7 | −0.13 | 0.7 | −0.17 | 0.6 | 0.2 | 0.5 | −0.04 | 0.9 |
| Primitive reflexes (baseline) | 0.438 | 0.03* | −0.5 | 0.1 | 0.01 | 1.0 | 0.75 | 0.01* | 0.57 | 0.08 |
| DLPFL (Left) (baseline)\[6\] | −0.53 | 0.05* | 0.47 | 0.09 | −0.27 | 0.4 | −0.6 | 0.02* | −0.46 | 0.1 |
| DLPFL (Right) (baseline)\[6\] | −0.4 | 0.1 | 0.24 | 0.4 | −0.26 | 0.4 | −0.36 | 0.2 | −0.32 | 0.3 |

*Significance at \(P<0.05\); \(r\) - Brain volume data was available for 14 patients as 3 MRI images could not be retrieved; SOFS – Social occupational functioning scale; DLPFL – Dorsolateral prefrontal lobe; MRI – Magnetic resonance imaging; MOTCO – Motor Coordination; SCOMP – Sequential complex motor performance; SENINT – Sensory integration

Need for comprehensive assessment of outcome measures
Our study found that baseline Left DLPFL volume and primitive reflexes predicts outcome as measured by SOFS but not the SCOS. Previous studies\[12-16\] have used the SCOS, GAF scale, disability assessment schedule (DAS) and quality of life scale as measures of outcome and these studies have yielded inconsistent results. The SCOS assess work, social contacts, duration of hospitalization, and absence of symptoms. Recent studies have emphasized the need for redefining outcome measures to include clinical improvement as well as social functioning.\[37\] The SOFS scale is one such scale which comprehensively assesses various domains of functioning such as Inter personal skills, social appropriateness and adaptive living skills. This study, demonstrates the importance of using comprehensive outcome measures in future prospective studies which can potentially yield consistent results.

Clinical implications
Schizophrenia can be associated with significant disability and hence markers for prediction of outcome at baseline prior to initiation of antipsychotic treatment can be of clinical importance. In this context, our study highlights the importance of NSS as a simple bedside test in assessment of schizophrenia patients. Presence of primitive reflexes at baseline would sensitize the clinician regarding need for possible early initiation of pharmacological interventions such as clozapine and intense psychosocial rehabilitation measures.

To the best of our knowledge this is the first study from India to look at baseline biological markers as predictors of long term outcome in schizophrenia. Some of the novel aspects of this study include (1) The sample assessed was antipsychotic naïve at baseline which controlled for effect of antipsychotics on both brain structure as well as NSS. (2) Outcome measures were comprehensively assessed using standardized as well as culturally validated scales measuring both clinical as well as socio-occupational functioning. A limitation of the study is that inter rater reliability could not be established between raters who...
assessed subjects at baseline and on follow-up. However, all brain morphometric analysis was done using coded images with the rater being blind to the status and during clinical and NSS assessments on follow-up the rater was blind to their scores at baseline.

To conclude this study highlights that (1) Primitive reflexes and smaller DLPI volume at baseline can predict poorer outcome on longitudinal follow-up in schizophrenia (2) NSS assessment can be a simple and useful bedside tool in assessment of schizophrenic patients (3) Comprehensive and multi-dimensional outcome measures should be used in future prospective studies which can yield more consistent results.

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