Comparison of Facial Emotion Recognition Deficits among Treatment-Responsive and Treatment-Resistant subjects with Schizophrenia

- A Case Control Study

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"COMPARISON OF FACIAL EMOTION RECOGNITION DEFICITS AMONG TREATMENT-RESPONSIVE AND TREATMENT-RESISTANT SUBJECTS WITH SCHIZOPHRENIA - A CASE CONTROL STUDY"** is a bonafide and genuine research work carried by me under the guidance of **Dr. Pradeep Palaniappan,** Associate Professor, Department of Psychiatry, PSGIMS & R, Coimbatore.

Place: Coimbatore **DR.PRATAP CHANDER PONRAJ.R**

Date:

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Place: Coimbatore

Date:

DR. PRADEEP PALANIAPPAN

Associate Professor

Department of Psychiatry

PSGIMS & R

Coimbatore

ENDORSEMENT BY THE HOD/DEAN OF THE INSTITUTION

This is to certify that this dissertation entitled **"COMPARISON OF FACIAL EMOTION RECOGNITION DEFICITS AMONG TREATMENT-RESPONSIVE AND TREATMENT-RESISTANT SUBJECTS WITH SCHIZOPHRENIA - A CASE CONTROL STUDY"** is a bonafide research work done by **DR.PRATAP CHANDER PONRAJ.R** under the guidance of **Dr. Pradeep Palaniappan,** Associate Professor, Department of Psychiatry, PSGIMS & R, Coimbatore.

Dr. RAMALINGAM, M.D.,
Dean,
PSGIMS & R,
Coimbatore.

DR. G. RAGHUTHAMAN, M.D.,
Professor and Head of department,
Department of Psychiatry,
PSGIMS & R,
Coimbatore.

Place : Coimbatore

Date :

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Dr.PRATAP CHANDER PONRAJ.R

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This is to certify that this dissertation work titled **"COMPARISON OF FACIAL EMOTION RECOGNITION DEFICITS AMONG TREATMENT-RESPONSIVE AND TREATMENT-RESISTANT SUBJECTS WITH SCHIZOPHRENIA - A CASE CONTROL STUDY"** of the candidate **Dr.PRATAP CHANDER PONRAJ.R** with registration Number: **201828302** for the award of Doctor of Medicine in the branch of Psychiatry. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion **88 pages** and result show **5%** of plagiarism in the dissertation.

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SA	**AmandaGarciaSousa_TFG.pdf** Document AmandaGarciaSousa_TFG.pdf (D47215067)	3
W	URL: https://www.mayoclinic.org/diseases-conditions/schizophrenia/diagnosis-treatment/d ... Fetched: 12/18/2020 8:51:00 AM	1
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W	URL: https://www.researchgate.net/publication/280909682_Patterns_of_Emotion_Attribution ... Fetched: 1/22/2020 8:08:21 PM	1
W	URL: https://www.researchgate.net/publication/221820249_Self-reported_empathy_deficits_ ... Fetched: 11/1/2019 2:33:03 PM	1
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SA	**All in one Dissertation.docx** Document All in one Dissertation.docx (D78558197)	2
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W	URL: https://www.researchgate.net/publication/6375014_Emotion_perception_and_social_ski ... Fetched: 3/4/2020 10:25:42 PM	3
W	URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5237235/ Fetched: 12/18/2020 8:51:00 AM	1
	URL: https://www.science.gov/topicpages/s/schizophrenia+group+showed	

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W	URL: https://www.researchgate.net/publication/234700011_Facial_emotion_recognition_in_p ... Fetched: 10/30/2019 11:38:17 AM	2
W	URL: https://www.researchgate.net/publication/50830981_Misreading_the_facial_signs_Spec ... Fetched: 12/12/2019 6:10:45 PM	1
SA	**CHAPTER 2-ONLY REVIEW OF LITERATURE.docx** Document CHAPTER 2-ONLY REVIEW OF LITERATURE.docx (D50109520)	1
SA	**1 to 6 Chapter.docx** Document 1 to 6 Chapter.docx (D83004108)	6
W	URL: https://www.science.gov/topicpages/c/chronic%2Bschizophrenia%2Bpatients.html Fetched: 11/16/2020 8:57:40 PM	2
W	URL: https://www.researchgate.net/publication/51591940_Deficits_in_social_cognition_A_m ... Fetched: 12/17/2020 12:15:39 PM	1

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POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : +91 422 - 4345818, Fax : +91 422 - 2594400, Email : ihec@psgimsr.ac.in

EC-CT-2018-0055

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To
Dr R Pratap Chander Ponraj
Postgraduate
Department of Psychiatry
Guide: Dr Pradeep Palaniappan
PSG IMS & R
Coimbatore

Ref: Project No.18/342

Date: December 29, 2018

Dear Dr Pratap Chander,

Institutional Human Ethics Committee, PSG IMS&R reviewed and discussed your application dated 05.12.2018 to conduct the research study entitled *"Comparison of facial emotion recognition deficits among treatment-responsive and treatment-resistant subjects with Schizophrenia - a case control study"* during the IHEC review meeting held on 20.12.2018.

The following documents were reviewed and approved:

1. Project Submission form
2. Study protocol (Version 1 dated 05.12.2018)
3. Informed consent forms (Version 2 dated 22.12.2018)
4. Data collection tool (Version 1 dated 05.12.2018)
5. Current CVs of Principal investigator, Co-investigators
6. Budget

The following members of the Institutional Human Ethics Committee (IHEC) were present at the meeting held on 20.12.2018 at Research Conference Room, PSG IMS & R between 9.30 am and 11.30 am:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Mr Antony Raj B	MA	Social Scinces	Male	No	Yes
2	Mrs Y Ashraf	MPT	Physiotherapy	Female	Yes	Yes
3	Dr. K. Bhuvaneswari	MD	Clinical Pharmacology	Female	Yes	Yes
4	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes
5	Dr A Jayavardhana	MD	Clinician (Paediatrics)	Male	Yes	Yes

SECRETARY PSG IMSR COIMBATORE INSTITUTIONAL HUMAN ETHICS COMMITTEE

6	Dr G Malarvizhi	M Sc, Ph D	Nursing	Female	Yes	No
7	Mr. R. Nandakumar (Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
8	Dr. Parag K Shah	DNB	Clinician (Ophthalmology)	Male	No	No
9	Mrs P Rama	M Pharm	Non-Medical (Pharmacy)	Female	Yes	Yes
10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gynaecology)	Female	Yes	Yes
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
12	Dr G Subhashini	MD	Epidemiology	Female	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mr. R. Shanmugam	MBA	Lay person	Female	No	Yes
15	Dr. D. Vijaya (Member – Secretary)	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

The study is approved in its presented form. The decision was arrived at through consensus. Neither PI nor any of proposed study team members were present during the decision making of the IHEC. The IHEC functions in accordance with the ICH-GCP/ICMR/Schedule Y guidelines. The approval is valid until one year from the date of sanction. You may make a written request for renewal / extension of the validity, along with the submission of status report as decided by the IHEC.

Following points must be noted:

1. IHEC should be informed of the date of initiation of the study
2. Status report of the study should be submitted to the IHEC every 12 months
3. PI and other investigators should co-operate fully with IHEC, who will monitor the trial from time to time
4. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to a colleague after obtaining clearance from HOD, Status report, including accounts details should be submitted to IHEC and extramural sponsors
5. In case of any new information or any SAE, which could affect any study, must be informed to IHEC and sponsors. The PI should report SAEs occurred for IHEC approved studies within 7 days of the occurrence of the SAE. If the SAE is 'Death', the IHEC Secretariat will receive the SAE reporting form within 24 hours of the occurrence
6. In the event of any protocol amendments, IHEC must be informed and the amendments should be highlighted in clear terms as follows:
    a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
    b. Alteration in the budgetary status should be clearly indicated and the revised budget form should be submitted
    c. If the amendments require a change in the consent form, the copy of revised Consent

Form should be submitted to Ethics Committee for approval

d. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented

e. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IHEC and only then can they be implemented

f. Any deviation-Violation/waiver in the protocol must be informed to the IHEC within the stipulated period for review

7. Final report along with summary of findings and presentations/publications if any on closure of the study should be submitted to IHEC

Thanking You,

Yours Sincerely,

SECRETARY

Dr Sudha Ramalingam
Alternate Member - Secretary
Institutional Human Ethics Committee

INDEX

ABSTRACT

Background: Though emotion recognition deficits had been consistently demonstrated in subjects with schizophrenia, most of the studies which showed emotion recognition deficits, had been done on first episode or chronic stable schizophrenia subjects, where they had grouped both treatment responsive & treatment resistant subjects without a priori definition of treatment resistance. Considering the evolving literature that treatment resistance could be a separate phenotypic subtype, cognitive deficits and social functioning needs to be systematically studied in a larger sample with a priori definition of treatment resistance.

Aim: To compare the Facial Emotion Recognition among patients with Schizophrenia who are treatment responsive and treatment resistant, in comparison with healthy controls; to compare the social functioning across the various groups and to find association if any, between facial emotion recognition and social functioning in patients with schizophrenia.

Methods: 3-arm cross sectional study with chronic stable, treatment responsive and resistant schizophrenia (DSM-5), matched with healthy controls. Assessment done through a single 90min interview using scales including SANS, SAPS, SUMD, MARS, GSDS-2, CAI, CGI-Cogs, GAF and CGI.

Results: No statistically significant differences was noted among the two schizophrenia groups in terms of accuracy and over-identification. Global social functioning and multiple individual domains were more impaired in subjects with schizophrenia when compared to healthy controls. Similarly subjects with treatment resistant schizophrenia showed more impairment in global and individual domains of functioning when compared to subjects with treatment resistant schizophrenia. Global functional impairment in subjects with treatment resistant schizophrenia had significant association with higher over-identification scores.

Conclusion: Facial Emotion Recognition Deficits seems to exist in Schizophrenia; but no major differences was noted in this area between treatment resistant and treatment responsive subjects with schizophrenia. Among subjects with treatment resistant schizophrenia, social functioning seems to be comparitively deficient, however comparitive studies with larger sample size and a more elaborate and objective assessment will help to get a better understanding about social functioning differences among treatment resistant and treatment responsive subjects.

Keywords: schizophrenia, resistance, responsive, social, cognition, functioning, facial, emotion, recogniton, correlation

INTRODUCTION

Schizophrenia is a severe psychiatric disorder that has a prominent effect on both the individuals affected and society. Schizophrenia is considered one of the most-disabling conditions among all diseases, in both the developing and the developed countries, and is associated with a decrease in social connections, reduced employment rates and impaired ability to live independently. It usually starts in young adulthood. Life expectancy is reduced by around 10 years, commonly as a consequence of suicide. Though the course of the illness today is considered more favourable than it was originally described, there is only a minority of those affected, who fully recover. The cumulative lifetime risk for men and women is similar, though it is higher for men in the age group less than 40 years.[1] The Global Burden of Disease Study reported that schizophrenia causes a high degree of disability, and that it accounts for 1.1% of the total DALYs (disability-adjusted life years) and 2.8% of YLDs (years lived with disability). According to the World Health Report [The WHO World Health Report: new understanding, new hope, 2001. Geneva], schizophrenia is shown as the 8th leading cause of DALYs worldwide in the age group 15-44 years.[2]

Schizophrenia is a chronic illness characterized by diverse psychopathology; the core features are the positive symptoms (delusions and

hallucinations; which are generally called psychotic symptoms in which contact with reality is lost), negative symptoms (reduced interests, impaired motivation, reduction in spontaneous speech, and social withdrawal), and cognitive impairment (patients had poorer performance than controls in many of the cognitive functions, both social and non-social cognitions, although much individual variability were reported). The use of operational criteria, such as those given in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the WHO International Classification of Diseases (ICD-10), has provided a reliable and uniform approach to psychiatric diagnoses.The positive symptoms tend to relapse and remit, though some patients can have residual long-term psychotic symptoms. The negative and cognitive symptoms are genreally more chronic and have been associated with long-term effects on social function[1].

Eight individual domains of cognitive impairment have been identified for schizophrenia according to the NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus[3]. Among them, seven (processing speed, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving and verbal comprehension) belong to the neurocognitive(NC) domain of functioning. Social cognition (SC) refers to the psychological processes that are involved in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves. This was later identified as an

additional domain.[4] Social cognition is a multi-dimensional construct which comprises of functions such as: (1) emotional processing (EP); (2) social perception and knowledge (SP); (3) theory of mind (ToM) and (4) attributional bias (AS)[5-8]. Apart from cognitive impairment, patients with schizophrenia also experience severe deficits in their daily functioning that get manifested within various areas, like independent living, the instantiation and maintenance of interpersonal relationships or vocational functioning and leisure[6,8,10-12]. One of the principal goals in schizophrenia research includes finding potentially treatable determinants of functional outcome.[13-17]

Individuals with schizophrenia have been shown to exhibit marked impairments in processing social information. This can result in misinterpretations of the social intent of others, social withdrawal and also impaired daily social functioning.[17,18] A larger understanding of these social cognitive impairments may hence provide opportunities for targeted recovery focused interventions. Furthermore, social cognitive impairments have been found to have trait-like qualities that precede the onset of illness. Thus, studies on social cognition in schizophrenia may also provide a better general insight into the mechanisms underlying the disorder[11,19]

In everyday life, individuals encounter numerous variety of social cues from others' faces, their voices and body movements that include gait, posture and gestures. The individual must perceive the social information through these

cues in order to make appropriate responses to others, thus facilitating social interactions. To date, studies on social cue perception in schizophrenia have largely focussed on the perception of faces and voices.[4]

A review of 22 studies[17] on social cognition and functional outcome established associations between social perception and knowledge, emotional processing and Theory of Mind and community functioning, social problem solving, social behavior in the milieu and social skills[8]. The individual effect sizes ranged from zero to large. However, the overall magnitude of the associations appeared small to modest. It has been suggested that social cognition functions as a mediator between neurocognition and outcome[20-26]. But it also appears to be a valid predictor by itself, as it explains additional variance in outcome that cannot be explained by neurocognition[21,27-30]. Other findings have showed that social cognition may even exceed the value of neurocognition and symptoms in explaining variance in outcome[31].

Day to day functioning is commonly impaired in schizophrenia, with deficits noted in the domains of social functioning, vocational performance, and performance of everyday activities[32]. Even among those patients who are classified as 'responders' to available pharmacological and psychosocial treatments, the disability rates are high and functional outcomes have changed minimally when compared to the success in treating psychosis[33].

The cognitive deficits and negative symptoms are thought to represent the main drivers of disability[34,35], although influences that are outside of the individual such as opportunities and disincentives like disability compensation meaningfully affect certain domains of functioning[35,36]. Usually the positive symptoms improve with treatment, or can otherwise be compensated for[37], but both cognitive deficits and negative symptoms receive minimal benefit despite the fact that current anti-psychotics control psychosis to the point that clinical remission rates are near 50% according to some studies[36]. Moreover, the negative and cognitive symptoms of schizophrenia, that are often present prior to the emergence of frank psychosis[38], appear to be related but separable domains with different functional implications[39,40]. Ventura et al. (2009) opined that the cognitive and negative symptoms both predict outcome, but they also note that negative symptoms partially mediate the longitudinal relationship between cognition and outcome, and therefore suggest that cognition has both direct and indirect effects on functioning[37]. Similarly, Lin et al. (2013) suggested that the negative symptoms mediate the influence of cognition on outcome[41].

Prior meta-analyses have suggested that the non-social cognitive deficits show less relation to social deficits when compared to the influence of social cognition[17,42], and researchers have found that the social deficits were less responsive to interventions that are aimed at treatment of cognition and functional skills deficits when compared to work and instrumental functions[43].

Finally, the achievement of different functional milestones (work, residence, and social achievements) is minimally inter-correlated in schizophrenia, suggesting that global indices of disability may lack the requisite specificity[44] and that different domains of everyday functioning are likely to have specific predictors of impairments.

REVIEW OF LITERATURE

Social Functioning in Schizophrenia:

Social functioning is a term used to describe self- or other report of interpersonal behaviors, behavior in the community settings (eg, skill ratings while shopping), skills of living independently (eg: self-care skills, grooming, financial skills, etc), ratings of social skill in a laboratory setting (eg: role-play tests), and ratings of various social problem-solving skills[8]. Deficits in social functioning, including communicating with others, maintaining employment, and functioning in the community, are observed in many disorders but are a defining feature of schizophrenia[45]. Indeed, social functioning deficits are evident pre-morbidly in those who later develop schizophrenia[46,47] and are often present in first-degree relatives of individuals with schizophrenia[48]. Impaired social functioning is also known to impact the quality of life[7] and predicts prognosis in schizophrenia, including relapse, poor course of the illness, and unemployment[49-51] Therefore, social dysfunction is a hallmark characteristic of schizophrenia that has major implications for the development, course, and outcome of this illness.

Social Cognition in Schizophrenia:

Whereas most previous research supports a significant relationship between at least one aspect of neuro-cognition - like processing speed, attention, learning and memory, problem solving and working memory- and functional

outcome, more recently, social cognition has been identified as a likely contributor to functional outcome[8]. A definition for social cognition given by Brothers[52] was ‘‘the mental operations underlying social interactions, which include the human ability and capacity to perceive the intentions and dispositions of others.’’ Likewise, Adolphs et al[53] in their paper, defined social cognition as ‘‘the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior.’’

Therefore, the theory implies that there exists a close association between social cognition and functional outcome since the ability to quickly process social stimuli is essential for social interactions, and problems in this area can impact different domains including peer, romantic, and family relationships as well as work/school behavior. Additionally, social cognition can also impact the functional outcome of independent living skills as accurately assessing social cues from the environment (eg: a person responding to body odor by increasing physical distance or making a disgusted facial expression), and having the social opportunities necessary to learn skills such as home and financial care, is usually a necessary prerequisite for making improvements in daily living skills[8].

Social cognition is a broad construct encompassing many abilities including emotion perception, social perception, theory of mind, and attributional style[19].

- Emotion Perception is the ability to infer emotional information (ie, what a person is feeling)from facial expressions, vocal inflections (ie, prosody), or some combination of these (ie, video clips).

- Social Perception refers to a person's ability to pick-up social cues from behavior provided in a social context, which includes but is not limited to, emotional cues. Social Perception is also closely tied to social knowledge, which refers to a person's comprehension of social rules and conventions (eg, as stored in social schemas); thus, these two abilities will be grouped together.

- Theory of Mind(ToM) involves both the ability to understand that others have mental states different from one's own and the capability to make correct inferences about the content of those mental states (eg, others' intentions or beliefs). Theory of Mind is typically explained as the participants' ability to understand false beliefs (first or second-order ToM) or the ability to understand verbal hints.

- Attributional Style refers to an individual's characteristic tendencies in explaining the causes of events in their lives. Prior research indicates that individuals having persecutory delusions and/or paranoia tend to blame others, more than situations, for negative outcomes. Within the domain of Emotion Perception, the most consistently used measure was the Facial Emotion Identification[8].

Relationship among Social Cognition domains and Functional Outcome:

Functional outcomes are usually assessed in the domains of social behavior in the milieu, community functioning, social skill, and social problem solving[8]. There is a fairly consistent relationship between Social Perception and various domains of functional outcome, particularly social problem solving, social behavior in the milieu, and community functioning. There is promising, but still inconsistent, evidence for a relationship between Social Perception and social skill. A number of recent studies have investigated whether Social Perception mediates the relationship between neurocognition and functional outcome. Specifically, Sergi et al[23] and Vauth et al[26] used path analysis and Structural Equation Modeling, respectively, to show that Social Perception does serve as a mediator between neurocognition and outcome, findings that have been replicated in another study that used multiple regression[20].

Emotion Perception is consistently associated with community functioning, and there is good support for a relationship with social behavior in the milieu and social skill as well. To the best of our knowledge, no study has examined the relationship between EP and social problem solving. There is preliminary evidence that Emotion Perception may mediate the relationship between neuro-cognition and functional outcome[21].

It is difficult to draw firm conclusions about the relationship between Theory of Mind and any one domain of functional outcome, since only few studies have examined the relationship between ToM and functional outcome[54], although there is some preliminary evidence that ToM is related to social behavior in the milieu, social skill and community functioning. However, these results clearly require replication.

Only 2 studies have examined Attributional Style and functional outcome. Lysaker et al[55] found that the number of stable attributions made was related to community functioning. Waldheter et al[30] found that having a ‘‘hostile attributional bias’’ predicted a small, yet significant amount of variance in aggression on an inpatient unit (i.e, social behavior in the milieu), even after accounting for previous violence history. Clearly, however, more research is required before confident conclusions can be drawn about the relationship of Attributional Style to functional outcome[8].

Social-Cognitive and Social-Perceptual Aspects of Theory of Mind:

Theory of Mind(ToM) is defined as the ability to understand other people’s mental states (e.g., beliefs, intentions) and ability to use this information to explain and predict their behavior[56]. Even though ToM dysfunction was first noted in autism and related conditions[57], subsequent work provided evidence for deficits in ToM in other neuropsychiatric conditions

including schizophrenia[54,58,59], affective disorders[60,61], brain injury[62], and fronto-temporal dementia[63].

Recent theories suggested that ToM concept is composed of 2 components: mental state decoding (social-perceptual) and mental state reasoning (social-cognitive)[64,65]. Mental state decoding component involves the ability to perceive mental states of others based on observable information like facial expressions or gestures. Although this concept is related to basic affect recognition, it also has a ToM component, which is not necessary for basic emotion recognition. Unlike recognition of basic emotions, recognition of more complex mental states depends on context; different meanings may be inferred from identical facial expressions in different situations. Mental state reasoning component involves the ability to integrate the contextual and historical information about a person (attitudes, knowledge,experiences) to understand behavior[56].

There is also increasing evidence that different aspects of ToM depend on different social brain networks[64,66]. Although orbito-frontal cortex and temporal cortex activation may be related to social-perceptual abilities, medial frontal cortex seems to be critical for the ability of reasoning about other's mental states[56].

Although affect recognition deficits are well known and widely investigated in schizophrenia[67,68], only some studies investigated social perceptual ToM abilities in schizophrenia[69,70]. ToM dysfunction was originally described as a state marker related to symptoms of schizophrenia, and several early studies, which included very small numbers of remitted patients, suggested that ToM is not impaired after symptom recovery[71,72]. There is now some evidence for trait-related ToM deficits in schizophrenia. Several studies demonstrated social-cognitive ToM deficits in remitted patients[73-75] and healthy relatives of patients[75]. several studies reported social-perceptual ToM deficits in symptomatic patients[69,70] and one study provides evidence for a deficit in social-perceptual aspect of ToM in stable patients with schizophrenia, suggesting that it may be important to include social-perceptual skills in rehabilitation programs in schizophrenia[56].

Neurocognitive Predictors of Social Cognition:

There is a general consensus that social cognition and neuro-cognition are related, but different constructs[7]. For example, research examining the neural underpinnings of neuro-cognitive and social cognitive abilities[53,66,76-79] suggest semi-independent systems for processing nonsocial and social stimuli. In addition, only a modest association appears to be there between social cognition and neuro-cognition[80-86]

Though Neurocognition and Social Cognition have been observed to exist as distinct cognitive constructs[87,88,89], an average of about 10% of shared variance exists between these two constructs[90]. Neurocognition and Social Cognition together, account for about a quarter of the variance in functional outcomes in schizophrenia[17]. Specifically, social cognition mediates the influence of neurocognition on functional outcome[91]. Emerging empirical evidence from longitudinal studies suggests that neuro-cognition underlies, and is causally primary to social cognition[92]. Investigators have explored the relationship between neurocognition and social cognition - a recent meta-analysis suggesting small to medium range non-specific correlations among different dimensions of these two constructs[93]. Basic neurocognition abilities including memory, executive functions and processing speed, among others, can underlie a rapid interpretation of complex social stimuli to inform the moment-to-moment generation, refinement and selection of models for thoughts and emotions of others, which underlie diverse social cognition abilities[94].

Only a few studies have assessed specific neurocognitive predictors of social cognition, by controlling for influence of other cognitive predictors. Early visual processing, and not other cognitive abilities like attention and working memory was found to have a significant association with emotion recognition and social perception[23,81] in schizophrenia. A NIMHANS study on 170 remitted subjects with schizophrenia[94] observed that higher social

cognitive processes like emotion recognition, faux pas recognition and social perception showed common neuropsychological correlates. Both executive functions and memory encoding processes predicted these social cognition processes, accounting for about 29% of the total variance. The prefrontal and medial temporal lobes might collectively contribute to such higher social cognitive processes. Cognitive flexibility, visual processing and encoding predicted the emotion-processing dimension of social cognition.

Facial Emotion Recognition Deficits in schizophrenia:

Over the years, studies on facial expression recognition in the general population have consistently reported that happy expressions are recognized faster and with better accuracy than any other basic emotional expression including anger, sadness, fear, disgust, and surprise[95-97]. Moreover, there is evidence of age associated changes in the accuracy with which negative and positive emotional expressions are recognized[98,99]

Facial emotion recognition deficits (FERD) have been consistently demonstrated in schizophrenia and are found to be specific for negative emotions of fear, anger, and disgust[68,82]. Few studies found a correlation between FERD and negative symptoms of alogia, apathy and affective flattening[100] and also positive symptoms of hallucinations and delusions[82,100,101]. In an Indian study done recently at NIMHANS, the team reported similar deficits in recognition of negative emotions in anti-psychotic naive

schizophrenia patients, which correlated with the severity of negative symptoms[102]. Recent literature also points out to significant association between emotional perception, emotion recognition and insight in schizophrenia subjects, but its association with social functioning had not been evaluated[103]. More importantly, poor insight can significantly affect the medication adherence and thereby may contribute to poor functioning as well[104].

It is not clear whether deficits in facial emotion identification in schizophrenic people are general or emotion specific[105]. While some studies found that patients with schizophrenia had generally impaired identification of emotion[106,107], other studies provided evidence of a selective impairment, with greater difficult in correctly identifying negative facial expressions of emotion such as fear, disgust and sadness[108,109]

The meta-analysis by Kohler et al[109] demonstrated robust effect sizes for deficits both in facial emotion identification as well as in differentiation in patients with schizophrenia. Along with magnitude of errors, patients with schizophrenia have also been demonstrated to have differential patterns of misidentification of emotional stimuli. Patients tend to misidentify neutral emotions as threat emotions such as anger[110]. Paranoia is known to be an essential feature of psychopathology in schizophrenia. Green and Phillips in their review have described heightened threat perception as a possible

mechanism for the development of persecutory delusions[111]. This is based on available evidence of differential emotion recognition in paranoid patients and attentional biases towards threat-related stimuli as demonstrated on attention tasks and visual scan path analysis. The authors describe a social threat perception model where schizophrenia is conceptualized as a disorder of enhanced threat perception[105].

The First Rank Symptoms (FRS) of schizophrenia as described by Schneider are important to the psychopathology of schizophrenia. It deals with deficits in the ownership and agency of one's thoughts, emotions and actions[113]. FRS, by their inherent nature are associated with an enhanced sense of paranoia and is experienced more commonly by patients of the paranoid subtype of schizophrenia. Paranoia has been described to be associated with enhanced threat perception and efficient identification of threatful facial emotional stimuli (anger)[114,115]. Hence patients experiencing FRS could form a homogenous subgroup of schizophrenia with a distinct pattern of emotion recognition deficits when compared with those schizophrenia patients who do not experience FRS[112].

Mirror neuron activity (MNA) dysfunction has been reported to underlie multiple symptoms of schizophrenia including negative symptoms, social cognition impairments, ego-boundary disturbances and catatonic symptoms[116]. These are specialized nerve cells that discharge during both passive observation

and active execution, i.e., “mirroring” of goal-directed motor acts[117], thus providing a system for matching observation and execution of motor actions[118] and hence, automatic behavior identification[119]. Functional magnetic resonance imaging (fMRI) studies in humans have demonstrated putative Mirror Neuron Activity (MNA) in the ventral premotor cortex, inferior frontal gyrus, inferior parietal lobule and insula[120]. These regions receive polysensory inputs through the posterior superior temporal sulcus[117]. It is hypothesized to underlie complex cognitive abilities like language, imitation, empathy and understanding goals of observed actions[121-124].

Three studies have examined the association between MNA and behavioral performance measures of different social cognition tasks. While three studies reported significant direct associations with social cognition tasks like theory of mind[89], attributional styles[125] and perspective taking ability[126], one study did not find any significant relationship between MNA and empathy[127]. The above mentioned studies that used SC task paradigms to assess MNA, found significant differences in MNA between patients and controls. These findings, in part, support the principles of embodied simulation[128], social projection[129] and perception-action coupling[130], that are grounded on the premise that mirror neurons become active ‘as if’ we were executing the exact action that we are observing, hence mediating social cognition. The role of mirror mechanisms can be extended further from understanding goals underlying motor actions to understanding other key aspects of human social

cognition, which include empathy and theory of mind. This is shown in the neural exploitation hypothesis. This hypothesis suggests that social cognition related abilities are produced by exploitation of brain mechanisms that have originally evolved for sensory-motor integration[128].

Neuroimaging findings related to FERD:

Face perception is considered the most-extensively studied aspect of social cue perception in schizophrenia[4]. The term "Non-affective face perception" involves the processing of non-emotional information from the faces of others (for eg, determining the sex, age or identity of a person) and is usually associated with increased activation in the bilateral fusiform face area (FFA), lateral occipital gyri, visual extrastriate cortex, anterior temporal pole and posterior superior temporal gyrus (pSTG). The FFA is also known as lateral fusiform gyrus[131,132]. The term "Affective face perception" involves processing of emotional expressions on the faces of others. It uses many of the same brain regions that are activated during non-affective face perception. In addition, affective face perception is associated with increased activation in limbic regions (amygdala, parahippocampal gyrus and posterior cingulate cortex), inferior frontal gyrus (IFG), medial prefrontal gyrus and putamen[132,133,134]. Behavioural studies that focussed on the non-affective face perception have shown that people with schizophrenia and healthy controls exhibit comparable performance in age- and sex-discrimination tasks, but the former have difficulty in matching and discriminating the identity of

individuals[135,136]. Therefore, people with schizophrenia have lesser difficulty with coarse judgments of facial features (like those used in determining the sex of an individual) and more difficulty with the more finer-grained judgments (like those used to determine an individual's identity). Several studies have shown that individuals with and without schizophrenia have similar levels of neural activation in the FFA during non-affective face perception[137,138]. However, patterns of neural activation across FFA voxels during a non-affective face-perception task were less cohesive in patients with schizophrenia[139], which could lead to poor performance on a relatively demanding non-affective face-perception task. In contrast, affective face perception has been found consistently to be impaired in people with schizophrenia.

One meta-analysis of studies using event-related potentials (ERPs) and four meta-analystic studies of functional magnetic resonance imaging (fMRI) have demonstrated that there is aberrant neural activity associated with affective face perception in individuals with schizophrenia compared with healthy individuals[140-144]. Though the fMRI meta-analyses also included some studies using other types of emotional stimuli, majority of the studies in the meta-analyses used face stimuli. One meta-analysis that focused on the amygdala showed that, when aversive emotional stimuli were contrasted with neutral stimuli, individuals with schizophrenia showed decreased amygdala activation as compared with healthy controls. This was not observed not when

aversive stimuli were presented alone[144]. The above finding suggests that the blunted response which is seen in the amygdala in people with schizophrenia during contrasts of emotional versus neutral conditions may be due to increased activation in response to neutral stimuli. The other three meta-analyses focused on areas beyond the amygdala[140-142]. Despite the differences in the approaches used for the meta-analysis, these studies indicate that, for affective face perception, people with schizophrenia show less activation in the right fusiform gyrus, right inferior occipital gyrus, hippocampal and left amygdala regions, medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC) and thalamus, but they show greater activation in the parietal lobule, insula, cuneus and superior temporal gyrus during affective face perception[140-142].

Studies using ERP to assess neural activation during face perception have focused on two components: N170 at occipito-temporal sites, which is associated with structural information of faces[145], and N250 at fronto-central sites, which is associated with facial emotional information. A meta-analysis of various schizophrenia studies revealed robust deficits in N170 and N250 components during affective face perception[143].

In summary, research on non-affective face processing in schizophrenia have reported conflicting results, while research on affective face processing in schizophrenia have been more consistent and have shown that people with schizophrenia demonstrate hypo-activation in brain regions that are associated

with affective face perception and hyper-activation in regions that are not typically associated with face perception. Thus, patients may recruit other areas to compensate for dysfunction in the key face-processing regions[4].

Comparison of FERD in early and late schizophrenia:

The study of social cognition[146,147] and emotion perception[148] in first-episode schizophrenia has shown evidence that impaired performance is present before the full expression of the disorder[149-153]. Several studies have compared emotion recognition performance in early stage and chronic schizophrenia patients, in an attempt to establish if these deficits are stable or vary over time[154].A pertinent question is present whether these deficits are state-related or are they trait markers of the disorder and persistent throughout the course of the illness. Studies that have examined facial emotion perception in the first degree relatives of people with schizophrenia demonstrated facial emotion recognition deficits in pro-bands of schizophrenia when compared to healthy controls. Longitudinal studies have also demonstrated that the FERD tend to remain stable over a follow up period of 12-months. This suggests that these deficits may be a trait marker for schizophrenia.

Cross-sectional studies comparing patients at different stages of the illness have shown deficits in facial affect recognition[148,155-157], usually reporting similar deficits in early and later stages. For example, Comparelli et al (2013)[148] found no differences among prodromal, first episode or multi-episode

schizophrenia patients when data were corrected for socio-demographic and clinical variables. In the same line, Vohs et al. (2014)[157] found no differences between first episode psychosis and prolonged psychosis groups in different measures of social cognition. Pinkham et al. (2007)[155] and Sachs et al. (2004)[156] also found deficits in emotion recognition tasks and emotion perception for patients of early and chronic schizophrenia. An exception to the above findings is the study done by Kucharska-Pietura et al. (2005)[106] who found more impairments in emotion perception in people with chronic schizophrenia.

Research on the differences in emotion recognition abilities between patients who are at different stages of the illness is of potential clinical relevance since there is evidence that performance impairment is specifically related to social competence and functioning on the early stages[158,159].Social cognitive remediation strategies that are designed to correct or improve this impairment should be in accordance with the deficits. If there were differences in facial emotion recognition at different stages of the illness the intervention should suit the specific deficits of each stage[154].

FERD and social functioning:

Kee *et al*.[160] studied the relationship between FERD and social functioning by applying the Strauss- Carpenter outcome scale and the role functioning scale which looks at work productivity, independent living, and relationships with family and friends with a follow- up assessment after 12 months. The

researchers reported a significant correlation between facial emotion recognition deficits and independent living and work functioning at baseline and at 12 months follow up. Even with adequate occupational skills and work place habits, the individuals' difficulty in understanding emotion in others could lead to an inappropriate responding which can affect their ability to successfully carry out job requirements. Horan *et al.*[161] in a 12-month longitudinal study found deficits in social cognition domains of emotion processing and theory of mind to be stable deficits over the course of illness. They reported an association between better performance on emotion recognition tasks and greater work performance and social functioning. Therefore, FERD is believed to have a direct impact on the socio-occupational functioning and have very important clinical relevance[162].

Role of anti-psychotics in FERD:

Some clinical studies suggest that atypical anti-psychotic drugs bring about improvement in cognitive symptoms, and that such improvement appears to be correlated with improvement of negative symptoms[163]. This cognitive improvement may be due to an increases in dopamine and acetylcholine in the prefrontal dorsolateral regions, and in parts of the hippocampus that are associated with acquiring and consolidating new information[164-166].

Several studies have evaluated the beneficial effect of atypical anti-psychotic drugs on emotional and cognitive functions in

schizophrenia[102,167,168]. Guilera et al.[169] presented a meta-analysis of 18 independent studies (N=1808) with the aim of exploring whether patients treated with second-generation anti-psychotic drugs obtain better results on cognitive functioning than those treated with first-generation anti-psychotic drugs. The results of their study showed that there was a mild improvement in the global cognitive index of patients treated with second-generation anti-psychotic drugs. These minor benefits were noted specifically in learning tasks and speed of processing. The effects are a little lower than those that were found in the meta-analysis by Woodward et al.[168], which concluded that people with schizophrenia receiving second-generation anti-psychotic drugs performed moderately better on neuropsychological tests than those treated with first-generation anti-psychotic drugs. By contrast, first-generation anti-psychotic drugs provided modest-to-moderate improvements in multiple cognitive domains[170]; particularly, some improvement in attention was recorded[171].

Studies on the influence of treatment with anti-psychotic drugs on emotion recognition has produced inconsistent results. Hempel et al[172]. reviewed the effects of anti-psychotic medication on facial affect recognition in schizophrenia according to 8 studies. No substantial difference was observed after treatment with either typical or atypical anti-psychotic drugs. A double-blind pilot study by Kee et al.[173] with random assignment to medication showed a benefit for risperidone in emotion perception, compared to

haloperidol in a small (N=20) study sample. In an open-label study without random assignment (N=52), Littrell et al.[174] found a benefit for olanzapine compared with a variety of first-generation medications on a social perception measure. Herbener et al.[175] found no benefit for risperidone on emotion perception in a small (N=13) crossover study of first-episode patients. A study with large sample size by Harvey et al.[176] showed that people with schizophrenia who were randomly assigned to risperidone (N=142) or quetiapine (N=124) did not improve significantly in emotion perception over the 8-week study period, with effect sizes of 0.11 and 0.14. The second-generation medications did not differ in their level of impact on emotion perception.

Important studies such as CATIE (Clinical Anti-psychotic Trials for Intervention Effectiveness), EUFEST (European First Episode Schizophrenia Trial), CUTLASS (Cost Utility of the Latest Anti-psychotic Drugs in Schizophrenia Study), TEOSS (Treatment of Early Onset Schizophrenia Spectrum Disorders) and other anti-psychotic trials have opined that neuro-cognitive improvements in patients treated with either first-generation or second-generation anti-psychotic drugs are minimal and that neither class of drug is inferior to the other[163]. Reduction in symptoms maybe associated with some benefit in patients with first-episode psychosis, but most of the cognitive improvement may have a practice effect, which is supplemented by the expectation of benefit[177-179].

FERD in Treatment Resistant Schizophrenia:

Kane et al., (1988) were the first to describe "Treatment Resistant Schizophrenia". The Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminologyidentified minimum and optimal criteria for "Treatment Resistant Schizophrenia", employing the following principles:

1. current symptoms of a minimum duration and severity determined by a standardized rating scale
2. ≥ moderate functional impairment
3. prior treatment consisting of ≥ 2 different antipsychotic trials, each for a minimum duration and dose
4. adherence systematically assessed and meeting minimum criteria
5. ideally at least one prospective treatment trial
6. criteria that clearly separated responsive from treatment resistant patients[180]

The percent of patients that fulfill these criteria ranges between 20% and 30%, a sub-population that comprises mainly males, characterized by more hospitalizations, earlier onset, and greater social and cognitive impairment compared to treatment-responsive patients[181].

Clozapine was found to be a drug for the treatment of TRS in a trial in comparison with chlorpromazine in patients operationally defined as treatment resistant and then started to be used worldwide in 1990[182]. Since then, extensive research has given enough evidence on the efficacy and effectiveness of clozapine in patients with TRS, and there is no arguement about the efficacy of clozapine in TRS and today clozapine is the drug of choice for treatment resistant schizophrenia, and it is recommended by all guidelines for the treatment of schizophrenia when patients do not respond to a certain number of trials with non-clozapine antipsychotics[183,184,185,186].

Patients with schizophrenia exhibit cognitive impairment that is 1-2 SDs below normal population scores[187]. Various cognition studies that compared patients with TRS with those with non-TRS was extensively reviewed by Woodward and Meltzer. They concluded that there is relatively little evidence to show that cognitive impairment is more severe in people with treatment resistant schizophrenia. Recently, however, De Bartolomeis and colleagues[188] compared 19 patients with TRS with 22 patients with non-TRS by using the Brief Assessment of Cognition in Schizophrenia. The team reported that patients with treatment resistant schizophrenia performed significantly worse in terms of verbal memory as well exhibited more severe levels of psychopathology as shown by the PANSS scores.

Role of Clozapine in FERD:

Clozapine has been reported to have beneficial effects on attention, verbal fluency, executive functions, and working memory[189,190]. In a study by Hallak et al. (2008)[191] that investigated neurocognitive functioning and facial emotion recognition in a sample of 15 treatment resistant schizophrenic patients treated with clozapine, they observed that compared to controls, patients spent more time to complete the ERT, with no differences in recognition accuracy or emotional intensity required for judging. The analysis of individual emotions showed a specific time-related deficit for the recognition of fear and disgust in patients. Regardless of this speed-related impairment, patients were as accurate as controls both in the ERT and the cognitive tests, with the same rates of correct answers. Given the amount of evidence regarding impaired emotion recognition and deficitary cognitive functioning in schizophrenia, the authors believe that the equivalence of accurate responses in both groups is enough to suggest that clozapine may be effective for treating consistently described neurocognitive and emotion recognition deficits in schizophrenia.

FERD and Electroconvulsive therapy :

Electroconvulsive therapy (ECT) is another form of treatment that is used for schizophrenia with catatonic features or with a past history of good response to ECT and also for treatment resistance to medication according to the treatment guideline from American Psychiatric Association[192]. In addition, the combination of antipsychotic drugs with ECT is related with rapid and

greater response in patients with schizophrenia[193]. Dalkiren et al., (2016)[194] aimed to to investigate the change in the ability of facial emotion recognition after ECT in thirty-two treatment resistant patients with schizophrenia. They observed that the rate of recognizing the disgusted facial expression increased significantly after ECT and no significant changes were found in the rest of the facial expressions (sadness, anger, happiness, surprise, fear, and neutral faces). Post-ECT, it was noted that the time period for response to happy and fearful facial expressions were significantly shorter.

Targeting FERD to improve funcitoning:

Impaired facial affect recognition may also contribute to both negative and positive symptoms[195]. They may be implicated in asociality[196], impaired emotional expression[197] and anhedonia[198-200]. Difficulty in interpreting emotions correctly could generate confusion regarding the intentions of others, which may lead to a confusing social world for people with psychosis[8]. Attempting to make sense of this may therefore trigger an increase in positive symptoms such as paranoia[8,111,201] and delusional ideation[202].Various interventions have been devised to try to improve facial affect recognition difficulties in psychosis. Kurtz and Richardson[203] carried out a meta-analysis of social cognitive remediation programmes, and reported a moderate to large effect size for improved identification (d = 0.78) and large effect size for improved discrimination (d = 1.01) of facial expressions.. A previous meta-analysis by Fett et al. (2011)[17] demonstrated that different domains of

social cognitive training programmes have different effects on components of social cognition and functioning.

The available literature suggest that improvements in social cognition lead to improvements in daily social functioning, which makes interventions such as the ones listed below essential in the quest for improvement in this area: *Training of Affect Recognition* (TAR)[204,205], *Emotion Management Training* (EMT)[206], *Psychological Integrate Therapy for Schizophrenia* (IPT)[207], *Cognitive Enhancement Therapy* (CET)[208], and *Social Cognition and Interaction Training* (SCIT)[209].

It is recommended that treatments targeting specific domains be examined to obtain a truer picture of the key active domains of social cognition that improve social functioning.Whether facial affect recognition training (FRT) improves facial affect recognition ability in people with schizophrenia and, by extension, improves social functioning needs to be researched. If FRT causes improvements in these domains, then it would be a valuable treatment for promoting recovery in psychosis. Bordon et al.,(2017)[195] conducted a meta-analysis of 8 randomised controlled trials (RCTs) consisting of 300 participants and concluded that facial affect recognition difficulties in schizophrenia are highly responsive to psychological interventions which were designed to improve them, and early evidence is present to show that this may lead to large gains in social functioning for this group – but not the symptoms.

The Training of Affect Recognition (TAR)[204] is a standardized Social cognition intervention program, and many studies have established the efficacy of TAR in improving performance on the social cognition domains[210-212]. A randomized controlled trial found a significant improvement in facial emotion recognition in persons with schizophrenia who received TAR intervention (N=28) in comparison to a cognitive remediation program (N=24) and treatment as usual (N=25)[213]. Another study reported that TAR intervention group showed improvements in facial emotion recognition, prosodic affect recognition, ToM and social competence when compared to group of schizophrenia who had received cognitive remediation program alone. TAR interventions have been found to have moderate to large effect sizes in improving facial emotion recognition in persons with schizophrenia[210,211]. The Indian version of the Training of Affect Recognition program was studied by Behere et al, (2017)[214] to demonstrate the feasibility of administering this intervention program in the Indian population.

FERD in other neuropsychiatric conditions:

FERD have also been found in other psychiatric disorders like bipolar affective disorder and body dysmorphic disorder[215]. Various neurological disorders have been documented to demonstrate FERD. Among patients who suffered from stroke, emotion recognition deficits have been noted to occur more in right hemispheric lesions and in isolated thalamic lesions. Deficits in

recognition of negative emotions are seen in early Alzheimer's disease and Fronto Temporal Dementia. It is hypothesized that these FERD could be related to some of the behavioral problems seen in people with dementia. Similar deficits in negative emotions of disgust and anger are also demonstrated in people with Huntington's disease. FERD has been well-demonstrated in Parkinson's disease, specially deficits in recognising disgust was noted among un-medicated patients and in those with associated cognitive impairment. Neuro-physiological studies show that there is under activation of amygdala in response to fearful stimuli in Parkinson's disease. Findings similar to the above have also been noted in patients with post encephalitic damage to the amygdala[215].

Tools for Assessment of Emotion Recognition:

The field of emotion recognition saw pioneering work done by Izard[216] and Ekman and Friesen[217]. They described the 6 basic human emotions of happy, sad, anger, fear, disgust and surprise and also first introduced a tool which contained a set of black and white photographs of posed emotions which was restricted in ethnicity and age. Over the years, similar tools were introduced- like the FEEL test, taken from the JACFEE series (Japanese and Caucasian Facial Expressions of Emotion). The Facial Discrimination Task (FDT)[218] which are a set of images of emotions expressed by trained actors developed at the university of Pennsylvania which were later validated. The Penn Emotion Recognition Test contains a set of 96 validated images made up

of 16 neutral images and 8 high and low intensity images for each of the basic emotions except surprise. A method of showing 3-dimensional images from 2-dimensional images has also been introduced for use in functional MRI studies(fMRI) of FERD. An inter-rater agreement of 60-80% between healthy volunteers has been generally accepted for the images used as stimuli in various studies in FERD. Only 2 studies have noted to use dynamic images i.e video clips as stimuli[215].

Need for a culturally sensitive emotion recognition assessment tool

Studies have shown that perception of emotion is influenced by ethnicity[219]. The major cultural difference that has been found is that Western cultures are more open when compared to the conservative Asian cultures; and that Americans tend to gauge emotional situations as more pleasant when compared to East Asians[220].

A meta-analysis studying the influence of cultural specificity of emotion recognition found an in group advantage, where emotions were recognized more accurately when they were both expressed and perceived by members of the same national or ethnic group[221]. A cross cultural study reported that, Indian people with schizophrenia and controls were found to perform poorly as compared to their American and German counterparts on tasks of emotion discrimination using facial expression of Caucasian actors[222]. The authors proposed that this was because the Indian study sample had unfamiliarity to the

Caucasian faces shown in the images. A more recent study; where groups of normal Indian, American and Japanese subjects viewed facial emotions expressed by actors of all 3 nationalities, supported this in group advantage[223]. Culture is also known to play a role in influencing course and outcome and planning of multidisciplinary treatments of mental disorders[224].

Therefore, data on FERD studies done on western population samples cannot be generalized as applicable for Indian patients. Studies have shown that female patients perform better on emotion recognition tasks and overall female faces are better recognized suggesting a sex difference in FERD[110]. Age of the individual also appears to play a role in influencing the emotion recognition. A study conducted among young bipolar patients found that they misidentified faces of same peer age group as angry, but similar error was not found with adult faces. Therefore, any tool that is used to study FERD should consider variations of sex and age on emotional expressions.

Tool for Recognition of Emotions in Neuropsychiatric Disorders-TRENDS

Given the influence of ethnicity, age and sex on emotional expression and perception and the need for stimuli capturing the dynamic, full color, fullchannel nature of emotional expressions for research in the field of FERD; it is imperative that a tool be developed for research in Indian patients. A team from NIMHANS has developed an advanced tool for emotion recognition

appropriate for research in Indian subjects namely – the ***T***ool for ***R***ecognitionof ***E***motions in ***N***europsychiatric ***D***isorder***S*** with the acronym – TRENDS[215].

Rationale for study

As seen in the above review of available literature, previous studies have demonstrated that,

- FERD is present in Schizophrenia during early and late stages
- FERD had not been investigated systematically in TRS
- No difference between FER in FGA and SGA
- No difference between anti-psychotics within same group
- Patients on Clozapine perform as accurately as healthy controls, with only delay in response time noted.

Though emotion recognition deficits had been demonstrated in schizophrenia subjects, most of the studies which showed emotion recognition deficits, had been done on chronic stable schizophrenia subjects, where they had grouped both treatment responsive & treatment resistant subjects without a priori definition of treatment resistance. This is of great importance, as there

are evolving literature that treatment resistance could be a separate phenotypic subtype based on clinical , neuroimaging, brain neurochemistry changes like lack of dopaminergic abnormalities, more glutamatergic abnormalities and decrease in grey matter when compared to treatment responsive schizophrenia subjects. Similarly in the wake of findings that while on clozapine, there are no statistical difference in facial emotion recognition between schizophrenia subjects and healthy controls, it needs to be systematically studied in a larger sample with a priori definition of treatment resistance. Such studies, using a culturally validated tool in Indian population would be the need of the hour for generalization to our Indian population.

AIM & OBJECTIVES

Aim:

Primary Aim:

- To compare the Facial Emotion Recognition among patients with Schizophrenia who are treatment responsive and treatment resistant, in comparison with healthy controls.

Secondary Aim:

- To compare the social functioning across the various groups.
- To find association if any, between facial emotion recognition and social functioning in patients with schizophrenia.

Objectives:

1. To find any statistical difference among the 2 treatment groups (Responsive and Resistant) and healthy controls in TRENDS accuracy score (TRACS) – Independent (happy, sad, anger, disgust, fear, surprise) & total; TRENDS over-identification score

2. To find any significant difference in social functioning (GSDS and GAF) and cognitive functioning (GAF-Cogs and CAI) scores across the 2 treatment groups and healthy controls.

3. To find any significant correlation between socio-demographic variables, illness variables, psychopathology scores (SANS, SAPS), insight scores(SUMD), level of compliance (MARS), emotional recognition (TRACS), social functioning (GSDS and GAF) and cognitive functioning (GAF-Cogs and CAI) scores.

Hypothesis:

H_0 (Null Hypothesis): There will be no difference noted in FER among patients with schizophrenia who are either treatment responsive or treatment resistant.

1. Treatment resistant schizophrenia subjects may have more facial emotion recognition deficits when compared to treatment responsive schizophrenia subjects.

2. Higher the facial emotion recognition deficits, poorer will be the social functioning in schizophrenia subjects even after controlling for confounders.

METHODOLOGY

Study Design: Cross-sectional study.

Study Area: PSG Hospitals, Peelamedu, Coimbatore, India

Study population: Stable out-patients, diagnosed to have Schizophrenia as per ICD-10 criteria by a qualified psychiatrist in PSG Hospital.

Sampling: Convenient sampling

Study period: From January 2019 to June 2020

Inclusion Criteria for subjects with Schizophrenia:

1. DSM-5 criteria (SCID -5)
2. Age 18 - 65
3. Both gender
4. On stable dose of oral anti-psychotic medication for at least 6 weeks.
5. On stable dose of depot anti-psychotic medication for atleast 6 months.
6. No hospitalization, no drug dose changes and no ECT received in the past 4 weeks.

Exclusion Criteria for subjects with Schizophrenia:

1. Co-morbid Intellectual Disability excluded by careful history & MSE
2. Co-morbid Axis-I psychiatric disorders (MINI 5.0)
3. History of neurological illness such as seizure disorder, head injury, CVA and neuro-degenerative diseases
4. History of substance dependence except nicotine & caffeine within last 6 months
5. Not fluent in tamil or english
6. Significant visual or hearing impairment
7. Unwillingness to participate in the study

Inclusion Criteria for Healthy Controls:

1. Consenting adults who are age and gender matched.
2. Psychiatric disorders ruled out by MINI 5.0

Exclusion Criteria for Controls:

1. Lifetime history of any psychiatric or neurological illness
2. Family history of psychiatric illness in first degree relatives
3. History of substance dependence except nicotine & caffeine within last 6 months
4. Not fluent in tamil or english
5. Significant visual or hearing impairment
6. Unwillingness to participate in the study

Sample Size and its Justification:

Using large effect size 0.4 {as reported in previous studies using TRENDS Tool in Indian schizophrenia population (Behere et al 2009, 2011)} , alpha of 0.05 and power at 80% the total sample size for the study is estimated to be 111 using the below mentioned formula.

$$n = \frac{2(Z_a + Z_{1-\beta})^{2}\sigma^{2},}{\Delta^2}$$

With the above justification, we decided to do a convenient sampling of 40 subjects with treatment responsive schizophrenia, 40 subjects with treatment resistant schizophrenia and 40 healthy controls.

Ethics clearance:

Ethics clearance was obtained from the Institutional Ethics Committee -PSGIMSR as per Indian Council of Medical research (ICMR) Ethical guidelines for biomedical research on human participants.

Project No. 18/342

DATA COLLECTION AND ASSESSMENT

The study protocol was explained to the participants, and a written informed consent was obtained from the patient. After recruiting the participants as per our inclusion and exclusion criteria, the participants along with a reliable informant underwent a single interview session lasting 90min during which time the following questionnaires and scales were applied.

Socio-demographic and Illness variables:

A semi-structured proforma was used to collect the following data from the participant, the reliable informant as well as from the available medical records.

- Socio-demographic variables including age, gender, education, occupation, marital status, socio-economic status as defined by the Modified Kuppusamy Scale, updated for the year 2018.
- Illness variables including age at onset of illness, total duration of illness, total duration of treatment, total duration of untreated psychosis and total number of days of hospitalization due to the current illness.
- Medication details including name of the oral drug/depot used and the current dosage.
- Chlorpromazine Equivalence and Olanzapine Equivalence were calculated from the given data as per the DDD Method- “Defined Daily Doses” given

by the World Health Organisation's Collaborative Center for Drug Statistics Methodology.[22]

- Details about use of nicotine and alcohol.

Symptomatology:

- "Scale for the Assessment of Positive Symptoms"(SAPS) was used to assess Positive Symptoms. It contains 34 items under 4 headings (hallucinations, delusions, bizarre behaviour, and positive formal thought disorder); each one rated from 0(none) to 5(severe). Symptoms are rated over the last month.The scale has an Inter-class Correlation Co-efficient of 0.98; Summary Scale Alpha of 0.77 and Composite Scale Alpha of 0.91[24 see proposal]

- "Scale for the Assessment of Negative Symptoms"(SANS)[23 see proposal sub]was used to assess Negative Symptoms. It contains 25 items under 5 headings (affective flattening, alogia, anhedonia/asociality, avolition/apathyand inattention); each one rated from 0(none) to 5(severe). Symptoms are rated over the last month. The scale has an Inter-class Correlation Co-efficient of 0.92; Summary Scale Alpha of 0.83 and Composite Scale Alpha of 0.92[24]

- "Scale to assess Unawareness of Mental Disease"(SUMD)[26] shortened version was used to assess the clinical insight. It is a semi-structured interview designed to assess 9 items of awareness on a 4 point scale(0-3). The shortened version of SUMD describes 3 dimensions: awareness of mental disorder [items

1-3], awareness of positive symptoms [items 4-6] and negative symptoms [items 5-9]. The Cronbach Alpha Score of internal consistency of the three dimensions were all at acceptable levels of ≥0.70. The scores of each dimension was obtained by summing the items within each dimension.

- "Medication Adherence Rating Scale"(MARS)[32] was used to assess the level of drug compliance. It is a self-report measure that can be administered in any clinical setting and is quick and simple. It contains 10 questions that require a Yes or No answer.The reliability analysis of the MARS using Crohnbach's alpha was 0.75. The internal validity of the MARS was assessed using IRT and suggested that it had a good internal validity.

Social and Cognitive Functioning:

- "Groningen Social Disabilities Schedule-II"(GSDS-II) was used to assess the socio-occupational functioning. This measure is based on social role theory and is compatible with the International Classification of Impairments. It was developed from the WHO-Disability Assessment Schedule (WHODAS-II); and is applicable across different cultures, as it takes the reference from each culture to assess a person's disability. There are a total of 22 items under 8 domains of functional roles (self-care, family, kinship, partner, parental, citizen, social and occupational roles). Each role ranged from 0(no impairment) to 3(severe impairment). A composite GSDS score was calculated as a mean of scores derived from the eight functional roles. In case a particular

role was not applicable and hence not assessed for a given participant (e.g., parental role for someone who did not have offspring), the mean scoring was calculated based on the number of applicable roles for that participant. The inter-rater reliability for the GSDS-II was excellent with intra-class correlation co-efficient ranging from 0.978 to 0.989.

- "Cognitive Assessement Interview"(CAI) was used for the assessment of cognitive functioning. It is a semi-structured interview that was developed from the CGI-CogS (Bilder et al., 2003) and the SCoRS (Keefe et al., 2006). The CAI contains 10 items based on six domains of cognitive functioning (working memory, attention-vigilance, verbal learning memory, reasoning and problem solving, speed of processing, social cognition). Each individual item rating and global rating is completed using a 7-point rating scales (with ratings from 1 to 7) with higher scores reflecting more impairment. The CAI involves making separate ratings based on the Patient interview, the Informant interview, and the Composite impression based on all available sources of information.

- "Global Assessment of Functioning - Cognition" (GAF-Cogs) is intended to supplement the CAI Global Severity rating, and parallels the DSM-IV GAF scale. The anchors listed correspond roughly to the GAF-CogS scores, with severity ratings 1 to 7 relating systematically to GAF-CogS scores from 100 to 1. It is recommend that this rating be provided based on

information from both patient and informant interviews, using all possible information about the patient's cognitive function.

Facial Emotion Recognition Deficits:

- "Tool for Recognition of Emotions in Neuropsychiatric Disorders" (TRENDS)[25] was used for the assessment of facial emotion recognition deficits. It is a tool containing 40 photographs taken using four trained actors (one young male, one young female, one older male, and one older female). Five basic expressions including happy, sad, fear, anger and neutral are shown through the photographs and the participants had to select their choice of the expression showed in each photograph. The photographs were shown on a 15-inch computer monitor at a distance of 1 metre. No time limit is given for the response. The individual entries are then fed into a calculation tool which gives the TRENDS Accuracy Score (TRACS) which is the number of correct responses by that participant. The TRENDS Over-Identification Score (TOI) is then calculated based on the total number of Neutral, Happy and Sad expressions recognized as Fear or Anger by each participant i.e. a non-threat emotion identifed as a threat emotion. The TRENDS tool was validated by 51 students and 5 qualified Psychiatrists from NIMHANS and had a good inter-rater agreement of 60%. The Cronbach Alpha Score of internal consistency was at 0.7

STATISTICAL ANALYSIS

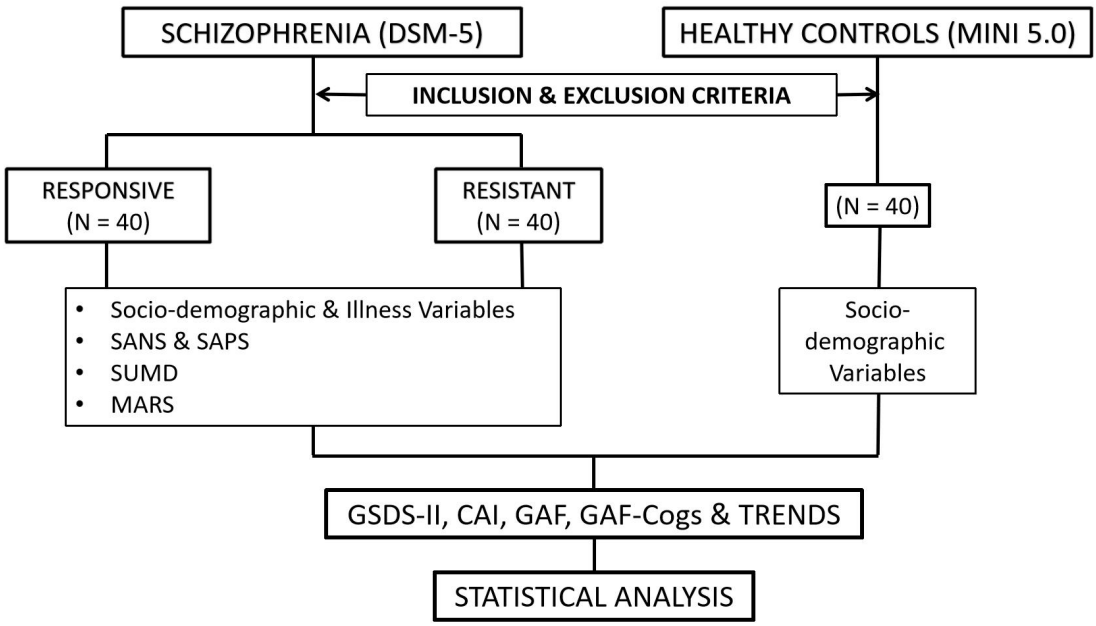
The data was tested for normality using Shapiro-Wilk test, which showed non- normal distribution. Essentially, the variables are compared as 2 groups, one being schizophrenia vs controls, and another group being subjects with treatment resistant schizophrenia vs treatment responsive schizophrenia.

While categorical socio demographic variables like education, occupation, marital status and socio economic status were compared among the groups using chi square test for any statistically significant difference, the continous variable like age of the participant was compared using Mann-Whitney U test, for statistically significant difference.

The TRENDS accuracy score, over-identification score, CAI severity scores, GAF-Cogs and social functioning scores were compared among the groups using Mann-Whitney U test for any statistically significant difference.

In order to understand the magnitude of difference in TRENDS accuracy, TRENDS over-identification, CAI severity scores, GAF-Cogs scores and GSDS scores among all three groups, Kruskal-Wallis test was used to assess whether variables significantly differ among the groups.

Further, the association among socio-demographic variables, illness variables, symptomatology scores, TRENDS accuracy scores, TRENDS over-identification scores, GSDS scores in each group, was tested using Spearman's rho correlation.



RESULTS

Socio-demographic variables:

The mean age was not statistically different (U = 1530.00; P = 0.416) between subjects with schizophrenia (mean rank = 62.04) (n = 73) and healthy controls (mean rank = 56.76) (n = 46). Similarly the mean age was not statistically different (U = 662.50 ; P = 0.978) between treatment responders (mean rank = 37.07) (n = 38) and treatment resistant subjects (mean rank = 36.93) (n = 35). There was no statistically significant difference in gender, education and marital status between subjects with schizophrenia and healthy controls; but a statistically significant difference was noted in occupation ($\chi 2$ = 26.40 ; P = <0.001) and in socio-economic status ($\chi 2$ = 10.73 ; P = 0.005), suggesting that the schizophrenia group had higher percentage of subjects who are unemployed (39 % in subjects with schizophrenia vs 17 % in healthy controls) and higher percentage of those who belong to lower socio economic status (85 % in subjects with schizophrenia vs 63 % in healthy controls) (Table 1).

There was no statistically significant difference in gender, marital status and socio-economic status between the treatment responders group and the treatment resistant group; but a statistically significant difference was noted in educational status ($\chi 2$ = 21.62 ; P = <0.001) and in occupation ($\chi 2$ = 34.64 ;

Table1 : Distribution of socio-demographic variables in study participants (n=119)

Characteristics	Schizophrenia vs Control		*U/χ2*	*p*	Responders vs Resistant		*U/χ2*	*p*
	Schizophrenia (N=73)	Control (N=46)			Responders (N=38)	Resistant (N=35)		
Age	62.04 (mean rank)	56.76 (mean rank)	1530.00*	0.416	37.07 (mean rank)	36.93 (mean rank)	662.50*	0.978
Gender								
Male	56 (76.7%)	28 (60.9%)	3.41**	0.065	28 (73.7%)	28 (80.0%)	0.41**	0.524
Female	17 (23.3%)	18 (39.1%)			10 (26.3%)	7 (20.0%)		
Edu.Status								
Mid.school	13 (17.8%)	6 (13.0%)			13 (34.2%)	0 (0.0%)		
High.school	32 (43.8%)	15 (32.6%)	3.39**	0.336	9 (23.7%)	23 (65.7%)	21.62**	**0.000**
Diploma	16 (21.9%)	12 (26.1%)			11 (28.9%)	5 (14.3%)		
Graduate	12 (16.4%)	13 (28.3%)			5 (13.2%)	7 (20.0%)		
Occupation								
Unemployed	29 (39.7%)	8 (17.4%)			7 (18.4%)	22 (62.9%)		
Elementary	8 (11.0%)	0 (0.0%)			1 (2.6%)	7 (20.0%)		
Plant/machine	8 (11.0%)	2 (4.3%)			8 (21.1%)	0 (0.0%)		
Craft/trade	10 (13.7%)	5 (10.9%)	26.40**	**0.000**	5 (13.2%)	5 (14.3%)	34.64**	**0.000**
Agri/fishery	2 (2.7%)	7 (15.2%)			2 (5.3%)	0 (0.0%)		
Shop/sales	9 (12.3%)	11 (23.9%)			8 (21.1%)	1 (2.9%)		
Clerks	3 (4.1%)	9 (19.6%)			3 (7.9%)	0 (0.0%)		
Technicians	4 (5.5%)	4 (8.7%)			4 (10.5%)	0 (0.0%)		
Marital Status								
Never married	36 (49.3%)	13 (28.3%)			14 (36.8%)	22 (62.9%)		
Married	29 (39.7%)	28 (60.9%)	6.84**	0.077	19 (50.0%)	10 (28.6%)	5.46**	0.141
Seperated	4 (5.5%)	1 (2.2%)			3 (7.9%)	1 (2.9%)		
Divorced	4 (5.5%)	4 (8.7%)			2 (5.3%)	2 (5.7%)		
SES								
Upper lower	30 (41.1%)	8 (17.4%)	10.73**	**0.005**	15 (39.5%)	15 (42.9%)	0.70**	0.706
Lower middle	32 (43.8%)	21 (45.7%)			16 (42.1%)	16 (45.7%)		
Upper middle	11 (15.1%)	17 (37.0%)			7 (18.4%)	4 (11.4%)		
Cur.Alcohol								
Yes	7 (9.6%)	11 (23.9%)	4.51**	**0.034**	6 (15.8%)	1 (2.9%)	3.52**	0.061
No	66 (90.4%)	35 (76.1%)			32 (84.2%)	34 (97.1%)		
Cur.Nicotine								
Yes	21 (28.8%)	15 (32.6%)	0.20**	0.657	11 (28.9%)	10 (28.6%)	0.00**	0.972
No	52 (71.2%)	31 (67.4%)			27 (71.1%)	25 (71.4%)		

*- Mann Whitney U, **- Chi square statistic; Cur.Alcohol - Current use of alcohol; Cur.Nicotine - Current use of nicotine

P = <0.001) suggesting that the treatment resistant group had higher percentage of subjects who studied upto high school (66 % of treatment resistant subjects vs 24 % of treatment responsive subjects) and a higher percentage of subjects who are unemployed (63 % of treatment resistant subjects vs 18 % of treatment responsive subjects) (Table 1).

Table 2: Illness variables among subjects with schizophrenia (n=73)

	Responders vs Resistant (mean rank)		*U*	*p*
	Responders (N=38)	Resistant (N=35)		
Age at onset of illness	42.67	30.84	449.50	**0.017**
Duration of illness	30.13	44.46	404.00	**0.004**
Duration of untreated psychosis	34.45	39.77	568.00	0.280
Chlorpromazine equivalence	36.66	37.37	652.00	0.885
Olanzapine equivalence	37.91	36.01	630.50	0.702
SANS Global	25.12	49.90	213.50	**0.000**
SAPS Global	25.41	49.59	224.50	**0.000**
SUMD	34.21	40.03	559.00	0.179
MARS	39.88	33.87	555.50	0.208
GAF	51.04	21.76	131.50	**0.000**

Footnotes: SANS- Scale for the Assessment of Negative Symptoms; SAPS- Scale for the Assessment of Positive Symptoms; SUMD- Scale to assess Unawareness of Mental Disorder; MARS- Medication Adherence Rating Scale; GAF- Global Assessment of Functioning

Illness variables:

Among the illness variables assessed, a statistically significant difference was noted in the duration of illness (U = 404.00 ; P = 0.004) between the treatment responders group and the treatment resistant group. Similarly, a statistically significant difference was noted in the SANS global scores (U = 213.50 ; P = <0.001); SAPS global scores (U = 224.50 ; P = <0.001); and GAF scores (U = 131.50 ; P = <0.001) (Table 2). These results suggest that subjects with treatment resistant schizophrenia had longer duration of illness, higher symptomatology (positive and negative) scores and poorer functioning when compared to subjects with treatment responsive schizophrenia.

TRENDS Tool Scores:

When subjects with schizophrenia were compared with healthy controls on FERD accuracy scores and over-identification scores, a statistically significant difference was noted in the overall TRACS (U = 196.50 ; P = <0.001); and TOI (U = 1087.50 ; P = 0.001) (Table 3), suggesting that subjects with schizophrenia had poor accuracy in identification of emotions and had over identified non threat emotions as threat emotions, when compared to healthy controls. However, there was no significant differences noted among the individual facial emotion identification.

Table 3: Comparison of Facial emotion recognition deficits among 2 groups (Schizophrenia vs controls & Treatment responders vs resistant schizophrenia)

	Schizophrenia vs Control (mean rank)		*U*	*p*	Responders vs Resistant (mean rank)		*U*	*p*
	Schizophrenia (N=73)	Control (N=46)			Responders (N=38)	Resistant (N=35)		
N_F	62.49	56.04	1497.00	0.066	36.46	37.59	644.50	0.715
N_A	61.39	57.79	1577.50	0.174	34.96	39.21	587.50	0.072
H_F	61.26	58.00	1587.00	0.108	36.92	37.09	662.00	0.933
H_A	60.32	59.50	1656.00	0.427	36.50	37.54	646.00	0297
S_F	63.56	54.35	1419.00	0.096	34.22	40.01	559.50	0.189
S_A	63.15	55.00	1449.00	0.009	36.87	37.14	660.00	0.926
TRACS	39.69	92.23	196.50	0.000	39.21	34.60	581.00	0.351
TOI	68.10	47.14	1087.50	0.001	34.74	39.46	579.00	0.320

Footnote: N_F- Neutral identified as Fear; N_A- Neutral identified as Anger; H_F- Happy identified as Fear; H_A- Happy identified as Anger; S_F- Sad identified as Fear; S_A- Sad identified as Anger; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score.

Table 4: Comparison of Facial emotion recognition deficits among 3 groups (Treatment resistant schizophrenia vs Treatment responsive schizophrenia vs healthy controls)

	Responders vs Resistant vs Control (mean rank)			χ^2	*p*
	Responders (N=38)	Resistant (N=35)	Control (N=46)		
N_F	61.54	63.53	56.04	3.58	0.167
N_A	58.07	65.00	57.79	6.28	0.043
H_F	61.13	61.40	58.00	2.60	0.273
H_A	59.50	61.20	59.50	2.40	0.301
S_F	59.26	68.23	54.35	4.46	0.108
S_A	62.90	63.43	55.00	6.83	0.033
TRACS	43.01	36.09	92.23	66.55	0.000
TOI	64.67	71.83	47.14	13.00	0.002

Footnote: N_F- Neutral identified as Fear; N_A- Neutral identified as Anger; H_F- Happy identified as Fear; H_A- Happy identified as Anger; S_F- Sad identified as Fear; S_A- Sad identified as Anger; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score.

Among the treatment responders and resistant subjects, there were no statistically significant differences noted among the two groups in terms of accuracy and over-identification (Table 3).

On comparing the FERD among all the three groups using Kruskal-Wallis test, statistically significant difference was noted in both the TRACS ($\chi 2$ = 66.55 ; P = <0.001) and TOI ($\chi 2$ = 13.00 ; P = 0.002) (Resistant > Responders > controls) (Table 4).

Subjective Cognitive Impairment Assessment:

The analysis suggested statistically significant differences exists between subjects with schizophrenia and healthy controls in CGI-Cogs score (U = 412.00 ; P = <0.001); GAF-Cogs score (U = 68.50 ; P = <0.001); and CAI score (U = 242.50 ; P = <0.001) (Table 5). The above findings imply that subjects with schizophrenia perceive higher impairment in the neurocognitive domain of functioning when compared to healthy controls.

Similarly, a statistically significant difference was noted between treatment responders and resistant subjects in CGI-Cogs score (U = 336.50 ; P = <0.001); GAF-Cogs score (U = 168.50 ; P = <0.001); and CAI score (U = 219.00 ; P = <0.001) (Table 5). This suggests that subjects with treatment resistant schizophrenia perceive higher impairment in the neuro-cognitive domain of functioning, when compared to subjects with treatment responsive schizophrenia.

Table 5: Comparison of subjective cognitive impairment among 2 groups (Schizophrenia vs controls & Treatment responders vs resistant schizophrenia)

	Schizophrenia vs Control (mean rank)		*U*	*p*	Responders vs Resistant (mean rank)		*U*	*p*
	Schizophrenia (N=73)	Control (N=46)			Responders (N=38)	Resistant (N=35)		
CGI-cogs	77.36	32.46	412.00	0.000	28.36	46.39	336.50	0.000
GAF-cogs	37.94	95.01	68.50	0.000	50.07	22.81	168.50	0.000
CAI	79.68	28.77	242.50	0.000	25.26	49.74	219.00	0.000
GAF	39.81	92.04	205.00	0.000	51.04	21.76	131.50	0.000

Footnote: CGIcogs- Clinical Global Impression-cognition; GAFcogs- Global Assessment of Functioning-cognition; CAI- Cognitive Assessment Interview; GAF- Global Assessment of Functioning

Comparison of subjective cognitive impairment among the three groups showed statistically significant difference in CGI-Cogs score ($\chi 2 = 59.99$; $P = <0.001$); GAF-Cogs score ($\chi 2 = 90.93$; $P = <0.001$); and CAI score ($\chi 2 = 81.50$; $P = <0.001$) (Table 6).

Table 6: Comparison of subjective cognitive impairment among 3 groups (Treatment resistant schizophrenia vs Treatment responsive schizophrenia vs healthy controls)

	Responders vs Resistant vs Control (mean rank)			$\chi 2$	*p*
	Responders (N=38)	Resistant (N=35)	Control (N=46)		
CGI-cogs	66.59	89.04	32.46	59.99	0.000
GAF-cogs	51.87	22.81	95.01	90.93	0.000
CAI	65.39	95.19	28.77	81.50	0.000
GAF	56.38	21.81	92.04	83.49	0.000

Footnote: CGIcogs- Clinical Global Impression-cognition; GAFcogs- Global Assessment of Functioning-cognition; CAI- Cognitive Assessment Interview; GAF- Global Assessment of Functioning

Global and Individual Social Functioning Scores:

A statistically significant difference was noted in the GSDS sum score (U = 747.50 ; P = <0.001) between subjects with schizophrenia and healthy controls, implying that global functioning was more impaired in subjects with schizophrenia when compared to healthy controls. Among individual domains, more deficits were noted in following areas of functioning; i.e; family role (U = 786.50 ; P = <0.001); partner role (U = 1084.50 ; P = 0.001); citizen role (U = 952.00 ; P = <0.001); social role (U = 632.00 ; P = <0.001); and occupational role (U = 1045.50 ; P = <0.001) (Table 7).

Table 7: Comparison of global social functioning and individual role behaviour scores among 2 groups (Schizophrenia vs controls & Treatment responders vs resistant schizophrenia)

	Schizophrenia vs Control (mean rank)		*U*	*p*	Responders vs Resistant (mean rank)		*U*	*p*
	Schizophrenia (N=73)	Control (N=46)			Responders (N=38)	Resistant (N=35)		
Self-care role	62.46	56.10	1499.50	0.254	30.72	43.81	426.50	0.003
Family role	72.23	40.60	786.50	0.000	25.63	49.34	233.00	0.000
Kinship role	64.32	53.15	1364.00	0.054	31.00	43.51	437.00	0.006
Partner role	68.14	47.08	1084.50	0.001	29.95	44.66	397.00	0.002
Parental role	57.88	63.36	1524.50	0.066	37.42	36.54	649.00	0.607
Citizen role	69.96	44.20	952.00	0.000	26.32	48.60	259.00	0.000
Social role	74.34	37.24	632.00	0.000	30.54	44.01	419.50	0.004
Occupational role	68.68	46.23	1045.50	0.000	27.09	47.76	288.50	0.000
GSDS sum score	72.76	39.75	747.50	0.000	24.61	50.46	194.00	0.000

Footnote: GSDS- Groningen's Social Disabilities Schedule II

When subjects with treatment resistant schizophrenia was compared with subjects with treatment responsive schizophrenia, the subjects with treatment resistant schizophrenia showed more impairment not only in global functioning [GSDS sum score (U = 194.00 ; P = <0.001)] but also in individual domains of functioning [self-care role (U = 426.50 ; P = 0.003); family role (U = 233.00 ; P = <0.001); partner role (U = 397.00 ; P = 0.002); citizen role (U = 259.00 ; P = <0.001); social role (U = 419.50 ; P = 0.004); and occupational role (U = 288.50 ; P = <0.001)] (Table 7).

Table 8: Comparison of global social functioning and individual role behaviour scores among 3 groups (Treatment resistant schizophrenia vs Treatment responsive schizophrenia vs healthy controls)

	Responders vs Resistant vs Control (mean rank)			χ^2	p
	Responders (N=38)	Resistant (N=35)	Control (N=46)		
Self-care role	52.21	73.59	56.10	10.80	0.005
Family role	55.95	89.90	40.60	45.16	0.000
Kinship role	54.58	74.89	53.15	11.65	0.003
Partner role	56.82	80.44	47.08	21.06	0.000
Parental role	58.55	57.16	63.36	3.53	0.172
Citizen role	52.84	88.54	44.20	38.91	0.000
Social role	65.07	84.41	37.24	42.83	0.000
Occupational role	51.54	87.29	46.23	36.01	0.000
GSDS sum score	53.79	93.36	39.75	50.13	0.000

Footnote: GSDS- Groningen's Social Disabilities Schedule II

Comparison of global social functioning and individual role behaviour scores among the three groups showed a statistically significant difference in the GSDS sum score($\chi 2$ = 50.13 ; P = <0.001); and also in the individual domains of self-care role ($\chi 2$ = 10.80 ; P = 0.005); family role ($\chi 2$ = 45.16 ; P = <0.001); kinship role ($\chi 2$ = 11.65 ; P = 0.003); partner role ($\chi 2$ = 21.06 ; P = <0.001); citizen role ($\chi 2$ = 38.91 ; P = <0.001); social role ($\chi 2$ = 42.83 ; P = <0.001); and occupational role ($\chi 2$ = 36.01 ; P = <0.001) (Resistant > Responders > Controls) (Table 8).

Correlation among illness variables and FERD in subjects with Treatment Resistant Schizophrenia:

Among the subjects who were diagnosed with treatment resistant schizophrenia, TOI was observed to have significant positive correlation with the SANS global score, which suggests that higher negative symptoms is associated with higher identification of non-threat emotions as threat emotions. Similarly, GSDS sum scores were observed to have significant positive correlation with the SANS global score, which suggests that higher negative symptoms were associated with higher deficits in social functioning (Table 9).

TOI was also found to have significant negative correlations with Chlorpromazine and Olanzapine equivalents. This probably suggests that higher doses of anti-psychotic medication were associated with lower over-identification (Table 9).

Functioning in subjects with Treatment Resistant Schizophrenia:

The correlation among illness variables, FERD and social functioning was evaluated using Spearman's rho correlation in subjects with treatment resistant schizophrenia. The TRENDS Accuracy scores appear to have a significant negative correlation with the SAPS global scores; whereas the TRENDS over-identification scores appear to have a significant positive correlation with the SANS global scores. These findings suggest that higher severity of positive symptoms was associated with lower accuracy in facial emotional identification. This association could be hypothesized that positive symptoms, by itself worsen facial emotion recognition deficits or that FERD significantly contributes to positive symptoms as well.

Similarly, subjects who had higher severity of negative symptoms had higher chance of over- identifying the non threat emotions as threat emotions. The GSDS sum scores were found to have a significant positive correlation with both the SANS global score as well as the TRENDS Over-identification scores, implying that global functional impairment in subjects with treatment resistant schizophrenia has significant association with higher severity of negative symptoms and higher rate of over-identification of non-threatful emotion as threat emotion (Table 9)

Table 9: Correlation among illness variables, symptomatology, FERD and global social functioning in treatment resistant schizophrenia (n=35)

	Current Age	Age at onset	Dx of illness	Dx of Rx	Dx of untreated psychosis	Total hosp stay	CPZ equiv	OLZ equiv	SANS global	SAPS global	TRACS	TOI	GSDS sum
Current Age	1.000	0.623**	0.850**	0.818**	0.433**	-0.181	-0.080	-0.080	-0.207	0.343*	0.200	-0.070	-0.282
Age at onset		1.000	0.153	0.132	0.100	-0.302	-0.212	-0.212	0.003	0.349*	0.061	0.170	0.020
Dx of illness(months)			1.000	0.969**	0.525**	0.026	0.014	0.014	-0.213	0.242	0.172	-0.125	-0.285
Dx of Rx(months)				1.000	0.335	-0.023	0.011	0.011	-0.114	0.275	0.145	-0.129	-0.239
Dx of untreated psychosis					1.000	0.234	0.123	0.123	-0.361*	-0.126	0.223	-0.068	-0.284
Total hosp stay(days)						1.000	0.294	0.294	-0.228	-0.384*	0.133	0.000	0.088
CPZ equiv							1.000	1.000**	-0.288	0.027	0.002	-0.615**	-0.200
OLZ equiv								1.000	-0.288	0.027	0.002	-0.615**	-0.200
SANS global									1.000	0.093	-0.058	0.498**	0.677**
SAPS global										1.000	-0.348*	0.023	0.250
TRACS											1.000	-0.093	-0.194
TOI												1.000	0.452**
GSDS sum													1.000

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed);
FERD- Facial Emotion Recognition Deficits; Dx- Duration; Rx- Treatment; CPZ- Chlorpromazine; OLZ- Olanzapine; SANS- Scale for the Assessment of Negative Symptoms; SAPS- Scale for the Assessment of Positive Symptoms; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score; GSDS- Groningen's Social Disabilities Schedule II

Table 10: Correlation among FERD and individual social role behaviours (GSDS) in treatment resistant schizophrenia (n=35)

	Self care	Family	Kinship	Partner	Parental	Citizen	Social	Occupational	GSDS sum	TRACS	TOI
Self care	1.000	0.186	-0.032	-0.120	0.278	0.354*	-0.114	0.343*	0.387*	0.033	0.250
Family		1.000	0.394*	0.274	0.129	0.167	0.207	0.387*	0.624**	-0.105	0.328
Kinship			1.000	0.495**	0.155	-0.067	0.000	0.020	0.475**	-0.503**	0.070
Partner				1.000	0.027	0.247	0.183	0.211	0.545**	-0.374*	0.200
Parental					1.000	-0.027	-0.295	0.276	0.197	-0.240	-0.009
Citizen						1.000	0.702**	0.426*	0.712**	0.028	0.324
Social							1.000	0.316	0.561**	0.126	0.340*
Occupational								1.000	0.645**	0.110	0.347*
GSDS sum									1.000	-0.194	0.452**
TRACS										1.000	-0.093
TOI											1.000

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed); FERD- Facial Emotion Recognition Deficits; GSDS- Groningen's Social Disabilities Schedule II; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score

On correlating with the individual domains of social functioning, the TRENDS Accuracy scores appear to have a significant negative correlation with the kinship and partner domains, suggesting that impairments in kinship and partner domains were associated with lower TRENDS Accuracy scores; whereas the TRENDS over-identification scores appear to have a significant positive correlation with the social and occupation domains, suggesting that social and occupational impairment was associated with higher over-identification scores. (Table 10).

A significant negative correlation seems to be present between TRACS and CAI and also between TOI and GAF-Cogs; and a significant positive correlation between TRACS and GAF-Cogs. This suggests that cognitive deficits are associated with lower accuracy as well as over-identification of emotions. (Table 14).

Correlation among illness variables and FERD in subjects with treatment responsive schizophrenia:

Among the subjects who were diagnosed with treatment responsive schizophrenia, the TRENDS Accuracy scores appear to have a significant negative correlation with the current age of the patient and the age at onset of illness; whereas the TRENDS over-identification scores appear to have a significant negative correlation with the total duration of illness and the total duration of treatment. There seems to be a significant positive correlation between the TRENDS over-identification and the total duration of hospital stay. The GSDS sum scores were found to have a significant positive correlation with both the SANS global scores and the SAPS global scores as well as the total duration of hospital stay, but not with facial emotional identification deficits (Table 11).

Table 11:Correlation among illness variables, symptomatology, FERD and global social functioning in treatment responsive schizophrenia (n=38)

	Current Age	Age at onset	Dx of illness	Dx of Rx	Dx of untreated psychosis	Total hosp stay	CPZ equiv	OLZ equiv	SANS global	SAPS global	GSDS sum score	TRACS	TOI
Current Age	1.000	0.703**	0.726**	0.660**	0.547**	-0.099	-0.166	-0.224	-0.010	0.180	-0.035	-0.365*	-0.139
Age at onset		1.000	0.196	0.125	0.371*	0.012	-0.130	-0.158	0.045	0.143	0.039	-0.375*	0.004
Dx of illness(months)			1.000	0.963**	0.573**	-0.155	-0.105	-0.158	-0.017	0.039	-0.047	-0.180	-0.380*
Dx of Rx(months)				1.000	0.377*	-0.131	10.173	-0.233	-0.065	-0.041	-0.095	-0.188	-0.418**
Dx of untreated psychosis					1.000	-0.075	0.110	0.114	0.215	0.208	0.152	-0.199	-0.095
Total hosp stay(days)						1.000	0.108	0.033	0.408*	0.247	0.463**	-0.061	0.458**
CPZ equiv							1.000	0.974**	0.120	-0.055	0.166	-0.083	-0.091
OLZ equiv								1.000	0.081	-0.097	0.158	-0.063	-0.101
SANS global									1.000	0.439**	0.913**	-0.139	0.066
SAPS global										1.000	0.408*	0.192	0.140
GSDS sum score											1.000	-0.089	0.083
TRACS												1.000	-0.136
TOI													1.000

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed);
FERD- Facial Emotion Recognition Deficits; Dx- Duration; Rx- Treatment; CPZ- Chlorpromazine; OLZ- Olanzapine; SANS- Scale for the Assessment of Negative Symptoms; SAPS- Scale for the Assessment of Positive Symptoms; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score; GSDS- Groningen's Social Disabilities Schedule II

Table 12: Correlation among FERD and individual social role behaviours (GSDS) in treatment responsive schizophrenia (n=38)

	Self care	Family	Kinship	Partner	Parental	Citizen	Social	Occupational	GSDS sum	TRACS	TOI
Self care	1.000	0.295	0.208	0.314	0.449**	0.338*	-0.041	0.535**	0.488**	0.034	-0.009
Family		1.000	0.252	0.245	0.180	0.214	0.138	0.449**	0.570**	0.345*	0.036
Kinship			1.000	0.723**	0.126	0.401*	0.334*	0.424**	0.678**	-0.250	0.187
Partner				1.000	0.251	0.665**	0.503**	0.432**	0.830**	-0.223	-0.046
Parental					1.000	0.300	-0.058	0.267	0.351*	0.200	-0.261
Citizen						1.000	0.469**	0.545**	0.732**	-0.201	0.327**
Social							1.000	0.327*	0.619**	-0.133	-0.009
Occupational								1.000	0.744**	-0.113	0.235
GSDS sum									1.000	-0.089	0.083
TRACS										1.000	-0.136
TOI											1.000

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed);
FERD- Facial Emotion Recognition Deficits; GSDS- Groningen's Social Disabilities Schedule II; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score

Functioning in subjects with Treatment Responsive Schizophrenia:

On correlating with the individual domains of social functioning, the TRENDS Accuracy scores appear to have a significant positive correlation with the family domain; which suggests that subjects with better functioning in the family domain have more accuracy in identifying emotions correctly. The TRENDS over-identification scores appear to have a significant positive correlation with the citizen domain (Table 12).

No significant correlations were observed between TRACS and TOI with the CGI-Cogs, GAF-Cogs and CAI (Table 14).

Functioning in the healthy control subjects:

On correlating with the individual domains of social functioning, the TRENDS Accuracy scores appear to have a significant negative correlation with the kinship domain, i.e. lower accuracy of identification was associated with higher deficits in the kinship domain. The TRENDS Accuracy scores also appear to have a significant negative correlation with the TRENDS over-identification scores (Table 13).

A significant negative correlation seems to be present for TRACS with CGI-Cogs and CAI. This is suggestive of lower accuracy scores associated with higher cognitive functioning deficits. (Table 14)

Table 13:Correlation among global social functioning, individual role-behaviors and FERD in healthy controls(n=46)

	Self care	Family	Kinship	Partner	Parental	Citizen	Social	Occupational	GSDS sum	TRACS	TOI
Self care	1.000	-0.015	0.475**	0.176	0.425**	0.533**	0.191	0.419**	0.556**	-0.103	-0.158
Family		1.000	0.178	0.307*	0.168	0.178	0.105	0.024	0.513**	-0.240	0.034
Kinship			1.000	0.403**	0.259	0.332*	0.329*	0.179	0.641**	-0.407**	-0.091
Partner				1.000	0.296*	0.111	0.300*	0.266	0.624**	-0.157	-0.040
Parental					1.000	0.378**	0.112	0.302*	0.487**	-0.231	-0.139
Citizen						1.000	0.424**	0.505**	0.637**	-0.269	0.080
Social							1.000	0.137	0.585**	-0.141	-0.178
Occupational								1.000	0.511**	-0.208	0.253
GSDS sum									1.000	-0.364*	-0.037
TRACS										1.000	-0.297*
TOI											1.000

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed);
FERD- Facial Emotion Recognition Deficits; GSDS- Groningen's Social Disabilities Schedule II; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score

Table 14: Correlation among FERD and subjective cognitive impairment in treatment resistant, treatment responsive schizophrenia and healthy controls

		CGI-cogs	GAF-cogs	CAI
TRACS	Responders	-0.113	-0.027	0.064
	Resistant	-0.245	0.408*	-0.470**
	Control	-0.357*	0.278	-0.295*
TOI	Responders	0.028	-0.203	0.317
	Resistant	0.379*	-0.352*	0.351*
	Control	0.165	-0.068	0.114

Footnote: *- Correlation is significant at the 0.05 level (2-tailed); **- Correlation is significant at the 0.01 level (2-tailed); FERD- Facial Emotion Recognition Deficits; TRACS- TRENDS Tool Accuracy Score; TOI- TRENDS Over-Identification Score; CGIcogs- Clinical Global Impression-cognition; GAFcogs- Global Assessment of Functioning-cognition; CAI- Cognitive Assessment Interview

DISCUSSION

Through our study, we observed significant deficits in Facial Emotion Recognition, especially accuracy and over-identification (non threat emotions are identified as threat emotions) among subjects with Schizophrenia who are both treatment responsive and treatment resistant, in comparison with healthy controls. Also, among subjects with treatment resistant schizophrenia, over-identification deficits are significantly associated with social functional impairment. However, there was no significant difference in accuracy or over-identification deficits among treatment resistant and treatment responsive schizophrenia, which supports our null hypothesis.

Over the years, it has been well-established that social cognition plays an important role in the various psychiatric disorders including schizophrenia. Currently, results of various studies suggest that social cognition is a mediator variable between basic cognition or neurocognition and social functioning[21,26].

Facial Emotion Recognition Deficits in Schizophrenia:

Our study findings suggest that subjects with schizophrenia had lesser accuracy in identification of emotions when compared to healthy controls. The findings in the area of emotional processing indicate that subjects with schizophrenia have a marked deficit in facial and vocal affect recognition[68,85,153,225,226]. A meta-analysis by Jani et al (2017) explored the

neurobiological basis for these defictis. Their analysis showed that in the subjects with schizophrenia, decreased activation was found in an extensive cluster incorporating the right ventrolateral PFC, cingulate, insula and subcortical regions including the amygdala, thalamus, caudate, lentiform nucleus and putamen; and increased activation in the parietal cortex extending to the inferior parietal lobule (IPL), postcentral gyrus, small clusters of the DLPFC,premotor areas and left cuneus. It is speculated that activation of these brain regions in subjects with schizophrenia, which are not usually recruited in healthy subjects, showed that these activation patterns may represent recruitment of accessory areas to compensate for inherent deficits in brain areas of facial recognition.

In general, these deficits in facial affect recognition occur in both recognition and discrimination[9]. Our study also showed this difference where we noted that the subjects with schizophrenia had over-identified non threat emotions as threat emotions.

It was also found in previous studies that happiness is the most easily recognized facial expression followed by surprise, and the judgment of fear is less accurate than other emotions[67]. We did find that there was a higher chance of identifying sad as anger in subjects with schizophrenia, when compared to controls, but no other over-identification deficits were identified. In our study, though neutral emotion was over-identified as fear emotion, it narrowly missed

significance in subjects with schizophrenia when compared to healthy controls. This is in line with previous study done on anti-psychotic naive schizophrenia by Behere et al (2011)[112] using the same instrument (TRENDS), which showed that subjects with first rank symptoms (FRS+) had higher over-identification errors when compared to subjects without first rank symptoms, (FRS-) and healthy controls. Our study showed no difference in under-identification errors in subjects with schizophrenia when compared to healthy controls. This is in contrast to the above mentioned study, which showed that individual emotions like fear, anger and disgust were under- identified in subjects with schizophrenia with or without FRS+ when compared to healthy controls. The difference could be related to medication effects in our study, while subjects of Behere et al (2011)[112] study were anti-psychotic naive.

In order to explain the abnormalities in emotional processing characteristic of schizophrenia, Aleman et al (2005)[227] proposed a model in which a dopamine imbalance is thought to underlie the increased emotional experience associated with psychosis, whereas structural volume reductions of the amygdala and reduced connectivity with the prefrontal cortex underlie the emotion perception deficit and the reduction in emotional expressive behavior. The authors also hypothesized that the central and basolateral nuclei of the amygdala may contribute differentially to these abnormalities.

FERD in Treatment resistant schizophrenia:

In this study, though the magnitude of TRENDS accuracy deficits in treatment resistant group was more when compared to treatment responsive group and healthy controls, there was no significant differences noted between the treatment responsive group and the treatment resistant group in accuracy, over-identification and under-identification scores. This is probably the first study to our knowledge, which has systematically compared FERD in treatment resistant schizophrenia with treatment responsive schizophrenia using relatively large sample when compared to earlier studies.

A Spanish case-control studied 14 subjects with treatment resistant schizophrenia (TRS) reported that the TRS group had lower scores on the recognition of facial and prosodic emotions. However an increased number of correct responses for the prosodic recognition of happiness was noted after an 8-week treatment with olanzapine. A Portugese 3-arm study with 10 normal controls, 10 subjects with treatment responsive schizophrenia and 10 subjects with treatment resistant schizophrenia reported that in emotion recognition, the treatment resistant group showed a lower number of correct responses and higher number of omissions than the other two groups; and this deficit correlated with the dose of neuroleptics, but the present study didn't show any significant relationship among chlorpromazine equivalents and FERD. Yet another case-control study[191] explored the facial emotion recognition in a sample of 15 treatment resistant schizophrenic patients treated with clozapine

(average daily dose - 470±73mg/day) and reported that patients spent more time to complete the emotion recognition tasks, specifically for fear and disgust. However, there were no differences in recognition accuracy or emotional intensity required for judging compared to the control group. This study expressed that the use of clozapine had helped in reducing FERD.

On the background of this study finding, we like to hypothesize that there was no significant difference in facial emotional recognition among treatment resistant and responsive schizophrenia, possibly secondary to potential FERD benefits of clozapine in the resistant group.. However, more studies are required to conclusively comment on the effect of clozapine on FERD. Future prospective studies looking into FERD deficits in treatment resistant schizophrenia at pre-clozapine and post-clozapine phases, will be able to delineate the role of clozapine on FERD deficits in treatment resistant schizophrenia.

Characteristics of Treatment resistant schizophrenia:

Comparing subjects with TRS versus subjects without TRS, few investigators found that subjects with TRS have earlier disease onset, predominance of the male gender and a higher number of hospitalizations.[228,229]. But in contrast, our study did not show any significant difference in age at onset of illness, gender and duration of hospital stay among subjects with and without TRS. We noted that the age of onset of illness, though not statistically

significant, was earlier in the treatment resistant group. This finding has been noted in previous studies also[230,231]. Other correlates such as duration of illness and history of substance abuse that have shown significant difference in another study[182] , did not show the same in our study. In the present study, the duration of illness and the duration of untreated psychosis were both longer in the treatment resistant group when compared with the treatment responsive group. Schennach et al (2012)[232]in their study had also noted longer duration of untreated psychosis in the treatment resistant group.

Contrary to expectations, we noted that the treatment resistant group had higher percentage of subjects who studied upto high school (66 % of treatment resistant subjects vs 24% of treatment responsive subjects). This could be because of convenient sampling strategy in which subjects who were relatively educated could have been selectively recruited. However, a higher percentage of subjects were unemployed (63% of treatment resistant subjects vs 18% of treatment responsive subjects), reflecting the impairment secondary to symptomatology, as corroborated in other studies.[233,234,235]

TRS patients have poorer outcomes when compared to other patients with severe mental illnesses. They also have worse achievement of functional milestones of everyday living[233] and the persistent positive, negative, and cognitive symptoms lead to worsened social functioning[234,235] and long-term disability[233,236,237].We observed that both the positive psychopathology (SAPS

Global) and the negative psychopathology (SANS Global) had statistically significant difference - the subjects with treatment resistant schizophrenia showed higher severity of positive and negative symptoms when compared to the treatment responsive group. However, no significant difference was observed in the dosage of medication among the two groups as seen by the Chlorpromazine and the Olanzapine Equivalents. Dosage of neuroleptics was not found to correlate with the social cognitive deficits in the study by Schneider et al., (1995)[85]. We also noted statistically significant difference in the GSDS, GAF, GAF-Cogs, CGI and CAI all of which suggest that subjects with treatment resistant schizophrenia have more subjectively perceived cognitive deficits and poorer social functioning when compared to subjects with treatment responsive schizophrenia.

FERD and influence on positive symptoms in schizophrenia:

Our study suggests that higher severity of positive symptoms was associated with lower accuracy in facial emotional identification in treatment resistant schizophrenia. This could be hypothesized that positive symptoms can directly worsen facial emotion recognition deficits or that FERD significantly contributes to the occurence of positive symptoms as well. However, we could not see such correlation with the treatment responsive category. Another Indian study was done by Behere et al (2009)[102] using the same TRENDS tool on anti-psychotic naive subjects with schizophrenia and reported that there was no

significant correlation between SAPS score and TRENDS over-identification score.

Based on evidence of differential emotion recognition in paranoid patients and attentional biases towards threat related stimuli, Green and Phillips, (2004)[111] described heightened threat perception as a possible mechanism for development of persecutory delusions. An Indian study[112] findings support this model of heightened threat perception in the evolution of psychopathology in schizophrenia patients. It is proposed that subjects with schizophrenia with FRS or other positive symptoms tend to over-identify non-threatful emotions as threatful emotions like fear and anger.

A meta-analysis on neuroimaging studies in schizophrenia[238] suggested that connectivity disruptions in local and external hippocampal circuits are important to the formation of psychotic symptoms and thought content; and that hippocampal hyperactivity leads to hyperdopaminergia in the striatum which may affect correct salience attribution and play a role in the development of hallucinations and delusions. Subjects with a high risk for developing psychosis have a disrupted relationship between hippocampal glutamate levels and striatal dopamine levels. Other studies have also showed that affective face perception is associated with increased activation in limbic regions including the amygdala and the parahippocampal gyrus.[132,133]. This could suggest that similar pathology can cause both positive symptoms as well as FERD.

In this study, there was nil significant correlation among positive symptoms and accuracy scores in treatment responsive schizophrenia. This is in line with previous studies which had shown efficacy of antipsychotics in reducing positive symptoms and improving facial recognition deficits. Giving support to this, are the findings from earlier studies that reported risperidone being beneficial in improving emotion recognition abilities[102,173]. Probably, the association could have been significant in antipsychotic naive schizophrenia, which needs further study.

FERD & negative symptoms:

Our correlation analysis showed a negative correlation between SANS global score and TRENDS Accuracy score, though it narrowly missed significance in treatment responsive schizophrenia. Higher severity of negative symptoms among the treatment resistant subjects was associated with poorer accuracy in facial emotion recognition. Similarly, subjects with treatment resistant schizophrenia showed TRENDS Over-Identification Scores having significant positive correlation with the SANS global score, which suggests that higher severity of negative symptoms is associated with higher over-identification of non-threat emotions as threat emotions. However, this association was not noted among the subjects with treatment responsive schizophrenia.

This finding was earlier shown in a meta-analysis[241] where meta-regression analysis indicated that negative symptoms were significantly associated with facial emotion performance, and that patients with severe negative symptoms were more impaired than patients with less severe negative symptoms (measured by the PANSS).Martin et al (2005)[239] in their study showed that the severity of the negative symptoms, especially affective flattening, avolition–apathy and inattentiveness, co-varied with deficits in facial processing; notably the higher these scores were, the greater the interference of identity on emotion matching. The correlation with the avolition–apathy subscore suggests that patients impaired in recognizing others' expressions are not able to interact with other people in social activities. In contrast, the attention impairment, could result in an overall decrease in the patients' performance.They also noted that the deficit in matching one emotion expressed by two distinct persons observed for subjects with schizophrenia co-varied with the severity of negative symptoms. Correlations between negative symptoms and some disabilities in facial emotion processing have already been reported by Silver et al., (2002)[240].

Patients with chronic schizophrenia that have marked negative symptoms present more deficits in their ability to recognize facial emotions and in their social skills than less chronic patients[9,28].Researchers state that there is evidence that patients in the acute phase of the disorder have poorer performance in affect recognition tasks than patients in the remission phase[242].

Complimenting the above findings, our study showed that longer duration of illness and longer duration of treatment were associated with higher rates of identifying non-threat emotions as threat emotions. Similarly, the younger age of the patient and a younger age at onset of illness appears to have more deficits in accurately identifying the facial emotions.

Influence of medications on FERD:

TOI was also found to have significant negative correlations with Chlorpromazine and Olanzapine equivalents among the treatment resistant group. This probably suggests that higher doses of anti-psychotic medication, especially clozapine, were associated with lower over-identification. A study investigating facial emotion recognition in a sample of treatment resistant schizophrenic patients treated with clozapine reported that, when compared to controls, these subjects with schizophrenia on clozapine spent more time to complete the task with no differences in recognition accuracy[191]. Apart from the above finding, we did not note any significant correlations between medications and the FERD in our study population.

It was consistently found that patients treated with risperidone performed better on facial affect recognition tasks than patients treated with haloperidol in three studies[81,244,245]. However, Hempel et al (2010)[172] in their review of eight articles summarised that neither typical nor atypical anti-psychotic medication has direct effects on the improvement in facial affect recognition abilities.

However, they may have indirect effects through the improvement of symptom severity or general cognition. Compared to the other case-control studies, our treatment responsive group did not have a homogenous anti-psychotic population and were not randomly assigned to a particular medication. Thus we were not able to decipher whether there was a differential effect of typical and atypical antipsychotics on FERD.

The main targets of most atypical anti-psychotic agents are the dopaminergic and serotonergic systems, which are extensively distributed throughout the mesocorticolimbic regions (amygdala, hippocampus, thalamus and anterior cingulate) and the frontal cortical area, known to be implicated in emotional processing[243]

FERD and social functioning:

In our study, we noted a statistically significant difference in the GSDS scale - which is used for evaluation of social functioning - between subjects with schizophrenia and healthy controls, implying that global social functioning was more impaired in subjects with schizophrenia when compared to healthy controls. Among individual domains, more deficits were noted in following areas of functioning- family role, partner role, citizen role, social role, and occupational role. The relationship between social cognition and functional outcome depends on the specific domains of each construct examined; however, it can generally be concluded that there are clear and consistent relationships

between aspects of functional outcome and social cognition[8]. It has been suggested that the deficits in affect perception are related to social functioning[28,246,247].

Similarly on comparing between the treatment responsive and treatment resistant groups, the subjects with treatment resistant schizophrenia showed more impairment not only in global functioning, but also in individual domains of self-care, family role, partner role, citizen role, social role and occupational role. It is suggested that, in schizophrenia, there may be a progressive deficit in emotional processing that may not seem to be related to specific symptoms but that is responsible for the social dysfunction observed in people suffering from this disorder[106]. The deficits in different domains of social functioning may not be secondary to the social cognitive deficits alone, but it can contribute to poor functioning along with neurocognitive factors as well as the severity of positive and negative psychopathologies.

Our study did not show any significant association among FERD and global social functioning in the treatment responsive group. The TRENDS Accuracy score however did show correlation with the family domain of functioning, in that better accuracy was correlating with better functioning within the family domain. The TRENDS Over-Identification score showed a positive correlation with the citizen domain. This could probably suggest that regular socialization and interaction with other people both within the family

and within the community can improve the facial emotion recognition deficits. This could in turn contribute to better global social functioning.On the other way, it is also possible, that subjects with more intact facial emotional recognition will be associated with better family & community functioning. Various studies on patients with Treatment Responsive Schizophrenia have found an association between cognition and social functioning[42,248-250]. Research carried out by Holthausen, Wiersma, Cahn et al. (2007)[16] found significant differences between patients with and without cognitive deficits in areas such as work and vocational functioning.

Similarly, GSDS sum scores were observed to have significant positive correlation with the SANS global score, which suggests that higher negative symptoms were associated with higher deficits in social functioning. In support of this finding, negative symptoms have been significantly associated with functional outcome[252] and ToM[71]. Leifker et al., (2009)[253]in his study, found that the negative symptoms in schizophrenia served as a mediator between functional capacity and real-world functioning behaviors. These findings suggest that if individuals with schizophrenia possess the necessary skills to function well in the community, negative symptoms may be predictive of whether they actually engage in these behaviors in the real-world. It is unclear whether negative symptoms are best thought of as a proximal cause to functioning behaviors (i.e., reflecting poor drive and motivation to perform the behaviors they are capable of) or a more distal cause affecting the ability to

correctly ascertain appropriate social and functional behaviors (i.e., causing impairment in social cognition and functional capacity)[40].

Influence of neurocognition over social cognition and functioning in schizophrenia:

Research carried out by Holthausen, Wiersma, Cahn et al. (2007)[16] found significant differences between patients with and without cognitive deficits in areas such as work and vocational functioning. It would seem that cognition is a more powerful indicator of work performance when there are cognitive deficits than when there are not. There is also evidence that neurocognitive capacity can be related to acquisition of social skills[254], to functioning in day-to-day activities[251] and to independent living. A review by Green et al. (2000)[42] of 39 published studies suggests that different types of cognitive deficits are associated with different areas of social functioning and that these cognitive deficits such as working memory, executive functioning, verbal memory and vigilancecould individually determine the functional performance of people with schizophrenia. Specific cognitive deficits such as those in could be associated with poor social functioning and with problems in social skill acquisition.This could explain the result of our study where we noted that the schizophrenia group had higher percentage of subjects who are unemployed (39% in subjects with schizophrenia vs 17 % in healthy controls) and higher percentage of those who belong to lower socio economic status(85 % in subjects with schizophrenia vs 63 % in healthy controls).

A high percentage of people with schizophrenia demonstrate some kind of cognitive deficit. According to Hoff, Sakuma, Wieneke et al. (1999)[255], they tend to be 1-2 SD below the performance of normal people. Our study also noted significantly more subjective cognitive deficits in patients with schizophrenia when compared with healthy controls. Nevertheless, it has to be pointed out that another study by Rund and Borg, (1999)[256] estimated 30% of schizophrenic patients do not exhibit any significant deficit in their cognitive or neuropsychological functioning.

Similar to other studies that have reported that patients with treatment resistant schizophrenia have more severe neurocognitive and social cognitive dysfunctions compared to treatment responsive patients[188,257,258], our study also showed a significant difference with more impairment noted in the treatment resistant group. Subjective cognitive deficits in the treatment resistant group appear to be associated with lower accuracy as well as over-identification of emotions, but not in treatment responsive group. Comparisons between the three study groups consistently showed significant differences in all the instruments that we used including GAF, Gaf-Cogs, CAI and CGI-Cogs. The impairment was maximum in the treatment resistant group followed by the treatment responsive group and then the healthy controls group.

Neurobiology of Treatment Resistant Schizophrenia:

Studies of patients with schizophrenia but not TRS specifically have found elevated striatal dopamine synthesis capacity, release, and baseline dopamine levels when compared to healthy controls. Demjaha et al., (2012)[259] found higher striatal DA synthesis capacity in non-TRS patients than TRS patients and healthy controls, and furthermore found no difference in DA synthesis capacity between TRS and healthy controls. TRS patients responsive to clozapine again were shown to have lower DA synthesis capacity than non-TRS, suggesting that a difference in DA synthesis capacity is a trait marker of TRS (reflecting different pathophysiology) rather than a state maker (related to symptom severity). These preliminary findings indicate the possibility that schizophrenia patients who respond to antipsychotics have higher levels of striatal DA synthesis, while TRS patients may not respond due to having physiologic levels of DA, and that Glu elevation and its associated excitotoxicity may instead account, at least in part, for the schizophrenic syndrome in TRS. However this hypothesis requires further exploration[260].

Data from neuroimaging studies indicates that TRS patients may have dopamine levels comparable to healthy controls as well as elevated glutamate concentration in anterior cingulate cortex, explaining in part why these patients are resistant to anti-dopaminergic medications. Furthermore, these imaging studies indicate that TRS and non-TRS may possibly arise from different pathophysiological mechanisms, reflected by differing brain changes like

greater gray matter reduction and increased white matter volume, suggesting that TRS may represent a subtype of schizophrenia[260].

Pharmacogenetic studies of clozapine have mainly focused on the neurotransmitters systems thought to be related to clozapine's efficacy. Single nucleotide polymorphisms (SNPs) in the *DRD1* gene, encoding the D1 receptor; *DRD2* gene, encoding the D2 receptor; *DRD3* gene, encoding the D3 receptor; and the 5-HT receptor system (HTR2A, HTR2C, and HTR6) have been identified as potentially related to response to clozapine[260].

As seen from the above studies, differences between treatment responsive schizophrenia and treatment resistant schizophrenia are not only observed neurocognition but also in neuroimaging and pharmacogenetics. These observations lends further support that treatment resistant schizophrenia is a separate phenotype.

Strengths of our study:

1. For the purpose of our study, we used a culturally adapted and well-validated instrument for the assessment of facial emotion recognition deficits which we consider as the major strength of our study.
2. To our knowledge, this is the first 3-arm study to have systematically compared FERD between treatment responsive schizophrenia and treatment resistant schizophrenia. We recruited only those patients who were at a chronic stable phase of the condition and on a stable dosage of medications.
3. We were able to recruit almost enough subjects as we originally calculated, and compared to similar case-control studies, our study appears to have a better sample size, hence giving more credibility to our findings.

Limitations of our study:

1. The findings of our study, may not be generalizable to the entire population as the participants were recruited from the subjects who were attending the OPD services of the tertiary care hospital, and thus will suffer from selection bias.
2. As we have focussed only on one domain of social cognition i.e facial emotion recognition, we are unable to comment about the role of other domains of social cognition as well as neurocognition. Thus, the role of neurocognition and other domains of social cognition in determining the social functioning could not be deciphered from this study.

3. The scales that we have used to evaluate cognitive deficits and social functioning are subjective, interview based and not performance based which may have given a more valid and objective interpretation.
4. Due to the nature of assessment, interviewer bias cannot be ruled out.

Conclusion:

In summary, the results of our study shows that Facial Emotion Recognition Deficits especially accuracy and identification deficits seems to exist in Schizophrenia; but no major differences was noted in FERD between treatment resistant and treatment responsive subjects with schizophrenia. Social functional impairment seems to be significantly associated with over-identification deficits in subjects with treatment resistant schizophrenia. However replicative studies using objective performance based measures of social functioning, measures to assess all domains of social cognition, neurocognition with larger sample size will help to get a better understanding about influence of these measures on social functioning among treatment resistant and treatment responsive subjects with schizophrenia. These types of studies will be highly helpful to decide on individualising treatment strategy in rehabilitation programmes aiming improvement in social functioning. Prospective studies focussing on pre-intervention and post-intervention differences in FERD could shed light on the effects of pharmacological or other non-pharmacological methods of treatment.

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ANNEXURES

Consent Form

பி.எஸ்.ஜி மருத்துவக் கல்லூரி

நிறுவன மனித ஒழுக்கவியல் குழு

ஆராய்ச்சி திட்டங்களுக்கு தகவல் அறியும் படிவம்

தேதி:

டாக்டர். பிரதாப் சந்தர் பொன்ராஜ்இ ஆகிய நான். பி.எஸ்.ஜி மருத்துவக் கல்லூரியின் மனநல மருத்துவத் துறையின் கீழ் "மனச்சிதைவு (ஸ்கிசோஃப்ரினியா) - சிகிச்சை பலனளிக்கும் மற்றும் சிகிச்சை பலனளிக்காத நோயாளிகளுக்கு இடையே உள்ள முக உணர்ச்சிகள் புரிதிறன் குறைபாடுகளை ஒப்பீடு செய்தல்" - என்ற தலைப்பில் ஆய்வு மேற்கொள்ள உள்ளேன்.

என் ஆய்வு வழிகாட்டி (மாணவர்களுக்கு மட்டும்) : டாக்டர். பிரதீப் பழனியப்பன். இணை பேராசிரியர், மனநல மருத்துவ துறை.

ஆய்வு மேற்கொள்வதன் அடிப்படை

மனச்சிதைவு பாதிப்பில் முக உணர்ச்சிகள் புரிதிறன் குறைபாடுகள் நிரூபிக்கப்பட்ட போதிலும், தற்போது கிடைக்கும் ஆய்வுகள், சிகிச்சை பலனளிக்கும் மற்றும் சிகிச்சை பலனளிக்காத மனச்சிதைவு நோயாளிகளின் பற்றாக்குறைகளை வரையறுக்கவில்லை. எனவே இந்த ஆய்வு இரண்டு ஆய்வு குழுக்களிடையே உள்ள வேறுபாடுகளை மதிப்பீடு செய்வதை நோக்கமாகக் கொண்டுள்ளது.

ஆய்வின் நோக்கம் :

- பல்வேறு படிநிலைகள் மற்றும் கேள்விகளைப் பயன்படுத்தி இரண்டு ஆய்வு குழுக்களிடையே எந்தவொரு புள்ளிவிவர வேறுபாடுகளையும் கண்டுபிடிக்க.
- முக உணர்ச்சிகள் புரிதிறன் குறைபாடுகள் மற்றும் சமூக செயல்பாடுகள் ஆகியவற்றுக்கு இடையேயான தொடர்புகளை ஆய்வு செய்ய.

ஆய்வில் பங்கு பெறுவோர் எண்ணிக்கை : *120 (40x3 குழுக்கள்)*

ஆய்வில் பங்கு பெறுவோர் மற்றும் வயது : 18 வயதிலிருந்து – 65 வரை

ஆய்வு மேற்கொள்ளும் இடம் :

பி.எஸ்.ஜி மருத்துவமனை. கோயம்புத்தூர்

ஆய்வு தொண்டர்கள் / பங்கேற்பாளர்கள்: *தகவல் அறிவிக்கும் எழுதப்பட்ட ஒப்புதல் பெறப்பட்ட, மனநல மருத்துவத் துறை வெளிநோயாளி பிரிவில் மனச்சிதைவு (ஸ்கிசோஃப்ரினியா) பாதிப்புடன் உள்ள நீண்டகால, நிலையான நோயாளிகள்.*

இந்த ஆய்வில் கிடைக்கும் தகவல்கள் ஐந்து வருடங்கள் பாதுகாக்கப்படும். இவை வேறு எந்த ஆய்விற்கும் பயன்படுத்தப்பட மாட்டாது. எந்த நிலையிலும் உங்களைப் பற்றிய தகவல்கள் யாருக்கும் தெரிவிக்கப்படமாட்டாது. அவை இரகசியமாக வைக்கப்படும்.

எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு.

ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சையில் எந்த வித மாற்றமும் இருக்காது.

இந்த ஆராய்ச்சிக்காக உங்களிடம் சில கேள்விகள் கேட்கப்படும். மேலும் இந்த ஆய்வில் பங்கு கொள்வது உங்கள் சொந்த விருப்பம். இதில் எந்த விதக் கட்டாயமும் இல்லை. நீங்கள் விருப்பப்பட்டால் இந்த ஆய்வின் முடிவுகள் உங்களுக்குத் தெரியப்படுத்தப்படும்.

ஆய்வு செய்யப்படும் முறை : நேர்காணல்

முதன்மை நேர்காணல் : *60-90 நிமிடங்கள்*

சுகாதாரக் கல்வி : பொருந்தாது

மருத்துவ பரிசோதனைகள் : இல்லை

இரத்த மாதிரி சேகரிப்பு : இல்லை

இரத்த மாதிரி எடுப்பது வழக்கமான சிகிச்சைக்காகவா அல்லது இந்த ஆய்விற்காகவா?

இல்லை

இதனால் ஏற்படக் கூடிய அசௌகரியங்கள் பக்க விளைவுகள்
இல்லை

இரத்த மாதிரிகள் ஆய்விற்கப் பின் பாதுகாத்து வைக்கப்படுமா? இல்லை

சேகரிக்கப்பட்ட இரத்தம் வேறு நிறுவனத்துடன் பகிர்ந்து கொள்ளப்படுமா? இல்லை

மருந்துகள் ஏதேனும் கொடுக்கப்படவிருந்தால் அவை பற்றிய விவரம் (கொடுக்கப்படும் காரணம் பக்க வளைவுகள் பயன்கள்) இல்லை

மருந்துகள் கொடுக்கப்படுவத வழக்கமான சிகிச்சை முறையா? இல்லை

கொடுக்கப்படும் மருந்துகளுக்கு மாற்று உள்ளதா? இல்லை

ஆய்வில் பங்கு பெறுவதால் ஏற்படும் பலன்கள்:

மனச்சிதைவு (ஸ்கிசோஃப்ரினியா) பாதிப்பில் நோயாளிகளுக்கு முக உணர்ச்சிகள் புரிதிறன் குறைபாடுகள்மற்றும் சமூக செயல்பாட்டிற்கும் இடையே உள்ள தொடர்பு குறித்து மருத்துவர்களிடையே விழிப்புணர்வை உருவாக்குவதன் மூலம், நோயாளிகளின் வாழ்க்கைத் தரத்தை உயர்த்துவதற்கு பொருத்தமான வழிமுறைகளை வகுக்க முடியும்.

ஆய்வில் பங்கேற்பதால் ஏற்படும் அசௌகரியங்கள் பக்க விளைவுகள்

இல்லை

ஆய்வின் முடிவுகள் எந்த முறையில் பயன்படுத்தப்படும்?

கல்வி சம்மந்தப்பட்ட கட்டுரைகளில் பங்கு கொள்ளவும் கருத்து பரிமாற்றம் செய்து கொள்ளவும்
பயன்படுத்தப்படும். இந்த ஆய்வின் கேள்விகளுக்கு பதிலளிப்பதிலோ தகவல்களை பரிமாறுவதாலோ உங்களுக்கு ஏதேனும் அசௌகரியங்கள் இருந்தால் எந்த நேரத்தில் வேண்டுமானாலும் ஆய்விலிருந்து விலகிக்கொள்ளும் உரிமை உங்களுக்கு உண்டு. எப்பொழுது வேண்டுமானாலும் ஆய்விலிருந்து விலகும் உரிமை உங்களுக்கு உள்ளது. ஆய்விலிருந்து விலகிக்கொள்வதால் உங்களுக்கு அளிக்கப்படும் சிகிச்சை முறையில் எந்த வித பாதிப்பும் இருக்காது என்று உங்களுக்கு உறுதியளிக்கிறோம். மருத்துவமனையில் நோயாளிகளுக்கு அளிக்கப்படும் சேவைகளை நீங்கள் தொடர்ந்து பெறலாம். இந்த ஆயிவல் பங்கேற்க ஒப்புக்கொள்ளுவதால் வேறு எந்த விதமான கூடுதலான பலனும் உங்களுக்குக் கிடைக்காது. நீங்கள் அளிக்கும் தகவல்கள் இரகசியமாக வைக்கப்படும். ஆய்வில் பங்கேற்பவர்கள் பற்றியோ அவர்கள் குடும்பதினை பற்றியோ எந்தத் தகவலும் எக்காரணம் . கொண்டும் வெளியிடப்படாது என்று உறுதியளிக்கிறோம். நீங்கள் அளிக்கும் தகவல்கள் அங்கீகரிக்கப்பட்ட ஆய்விற்கு மட்டுமே பயன்படுத்தப்படும். இந்த ஆய்வு நடைபெறும் காலத்தில் குறிப்பிடத்தகுந்த புதிய கண்டுபிடிப்புகள் அல்லது பக்க விளைவுகள் ஏதும் ஏற்பட்டால் உங்களுக்குத் தெரிவிக்கப்படும். இதனால் ஆய்வில் தொடர்ந்து பங்கு பெறுவது பற்றிய உங்கள் நிலைப்பாட்டை நீங்கள் தெரிவிக்க ஏதுவாகும்.

ஆய்வுக்குட்படுபவரின் ஒப்புதல் :

நான் இந்த ஆராய்ச்சியின் நோக்கம் மற்றும் அதன் பயன்பாட்டினைப் பற்றி தெளிவாகவும். விளக்கமாகவும் தெரியப்படுத்தப்பட்டுள்ளேன். இந்த ஆராய்ச்சியில் பங்கு கொள்ளவும். இந்த ஆராய்ச்சியின் மருக்துவ ரீதியான குறிப்புகளை வரும் காலத்திலும் உபயோகபடபடுத்திக் கொள்ளவும் முழு மனதுடன் சம்மதிக்கிறேன்.

ஆய்வுக்குட்படுபவரின் பெயர். முகவரி :

தேதி :

ஆய்வாளரின் கையொப்பம் :

தேதி :

ஆய்வாளரின் தொலைபேசி எண் : 9655299617
நெறிமுறை குழு அலுவலக தொலைபேசி எண் : 0422 – 2570170 உள்தொடர்பு எண் : 5818

SOCIO-DEMOGRAPHIC DETAILS

- Category of Study: Responsive / Resistant / Control
- Age: Gender:
- Education: Occupation:
- Marital Status: SES (Mod.Kuppusamy Scale 2018):
- Age at onset of illness:
- Duration of illness(months):
- Duration of treatment:
- Drug used at present:……Dosage:…… since…….
- Days of prior hospitalization:
- Duration of untreated psychosis:
- Current alcohol use:
- Current nicotine use:

Sr. No.	Occupation of the Head	Score
1	Legislators, Senior Officials & Managers	10
2	Professionals	9
3	Technicians and Associate Professionals	8
4	Clerks	7
5	Skilled Workers and Shop & Market Sales Workers	6
6	Skilled Agricultural & Fishery Workers	5
7	Craft & Related Trade Workers	4
8	Plant & Machine Operators and Assemblers	3
9	Elementary Occupation	2
10	Unemployed	1

(b)Education of the Head of the Family: -

Sr. No.	Education of the Head	Score
1	Profession or Honours	7
2	Graduate	6
3	Intermediate or diploma	5
4	High school certificate	4
5	Middle school certificate	3
6	Primary school certificate	2
7	Illiterate	1

(c)Total Monthly Income of the Family: -

Sr. No.	Updated Monthly Family Income in Rs. (2012)	Updated Monthly Family Income in Rs. (2016)	Updated Monthly Family Income in Rs. (2018)	Score
1	>30375	≥ 40,430	>126,360	12
2	15188-30374	20,210–40,429	63,182-126,356	10
3	11362-15187	15,160–20,209	47,266-63178	6
4	7594-11361	10,110–15,159	31,591-47262	4
5	4556-7593	6060–10,109	18,953-31589	3
6	1521-4555	2021–6059	6327-18949	2
7	≤1520	≤ 2020	≤6323	1

(d)Kuppuswamy's Socio-Economic Status Scale 2018: -

Sr. No.	Score	Socioeconomic Class
1	26–29	Upper (I)
2	16–25	Upper Middle (II)
3	11–15	Lower Middle (III)
4	5–10	Upper Lower (IV)
5	< 5	Lower (V)

SANS

0=None	1=Questionable	2=Mild	3=Moderate	4=Marked	5=Severe

1-12 dupl

0. CARD NUMBER [_ _] 13-14

1. AFFECTIVE FLATTENING OR BLUNTING

1 **Unchanged Facial Expression** [_] 15
The patient's face appears wooden —changes less than expected as emotional content of discourse changes.

2 **Decreased Spontaneous Movements** [_] 16
The patient shows few or no spontaneous movements, does not shift position, move extremities, etc.

3 **Paucity of Expressive Gestures** [_] 17
The patient does not use hand gestures, body position, etc, as an aid in expressing his ideas.

4 **Poor Eye Contact** [_] 18
The patient avoids eye contact or "stares through" interviewer even when speaking.

5 **Affective Nonresponsiveness** [_] 19
The patient fails to laugh or smile when prompted.

6 **Inappropriate Affect** [_] 20
The patient's affect is inappropriate or incongruous, not simply flat or blunted.

7 **Lack of Vocal Inflections** [_] 21
The patient fails to show normal vocal emphasis patterns, is often monotonic.

8 **Global Rating of Affective Flattening** [_] 22
This rating should focus on overall severity of symptoms, especially unresponsiveness, eye contact, facial expression, and vocal inflections.

2. ALOGIA

9 **Poverty of Speech** [_] 23
The patient's replies to questions are restricted in amount, tend to be brief, concrete, unelaborated.

10 **Poverty of Content of Speech** [_] 24
The patient's replies are adequate in amount but tend to be vague, overconcrete or overgeneralized, and convey little in information.

11 **Blocking** [_] 25
The patient indicated, either spontaneously or with prompting, that his train of thoughts was interrupted.

12 **Increased Latency of Response** [_] 26
The patient takes a long time to reply to questions; prompting indicates the patient is aware of the question.

13 **Global Rating of Alogia** [_] 27
The core features of alogia are poverty of speech and poverty of content.

0=None	1=Questionable	2=Mild	3=Moderate	4=Marked	5=Severe

3. AVOLITION – APATHY

14 Grooming and Hygiene [_] 28
The patient's clothes may be sloppy or soiled, and he may have greasy hair, body odor, etc.

15 Impersistence at Work or School [_] 29
The patient has difficulty seeking or maintaining employment, completing school work, keeping house, etc. If an inpatient, cannot persist at ward activities, such as OT, playing cards, etc.

16 Physical Anergia [_] 30
The patient tends to be physically inert. He may sit for hours and not initiate spontaneous activity.

17 Global Rating of Avolition – Apathy [_] 31
Strong weight may be given to one or prominent symptoms if particularly striking.

4. ANHEDONIA – ASOCIALITY

18 Recreational Interests and Activities [_] 32
The patient may have few or no interests. Both the quality and the quantity of interests should be taken into account.

19 Sexual Activity [_] 33
The patient may show decrease in sexual interest and activity, or enjoyment when active.

20 Ability to Feel Intimacy and Closeness [_] 34
The patient may display an inability to form close or intimate relationships, especially with opposite sex and family.

21 Relationships with Friends and Peers [_] 35
The patient may have few or no friends and may prefer to spend all his time isolated.

22 Global Rating of Anhedonia – Asociality [_] 36
This rating should reflect overall severity, taking into account the patient's age, family status, etc.

5. ATTENTION

23 Social Inattentiveness [_] 37
The patient appears uninvolved or unengaged. He may seem "spacey".

24 Inattentiveness During Mental Status Testing [_] 38
Test of "serial 7s" (at least five subtractions) and spelling "world" backwards. Score 2 = 1 error, score 3 = 2 errors, score 4 = 3 errors.

25 Global Rating of Attention [_] 39
This rating should assess the patient's overall concentration, clinically and on tests.

SAPS

0=None 1=Questionable 2=Mild 3=Moderate 4=Marked 5=Severe

1-12 dupl

0. CARD NUMBER [_ _] 13-14

1. HALLUCINATIONS

1 Auditory Hallucinations [_] 15
The patient reports voices, noises, or other sounds that no one else hears.

2 Voices commenting [_] 16
The patient reports a voice which makes a running commentary on his behavior or thoughts.

3 Voices Conversing [_] 17
The patient reports hearing two or more voices conversing.

4 Somatic or Tactile Hallucinations [_] 18
The patient reports experiencing peculiar physical sensations in the body.

5 Olfactory Hallucinations [_] 19
The patient reports experiencing unusual smells which no one else notices.

6 Visual Hallucinations [_] 20
The patient sees shapes or people that are not actually present.

7 Global Rating of Hallucinations [_] 21
This rating should be based on the duration and severity of the hallucinations and their effects on the patient's life.

2. DELUSIONS

8 Persecutory Delutions [_] 22
The patient believes he is being conspired against or persecuted in some way.

9 Delusions of Jealousy [_] 23
The patient believes his spouse is having an affair with someone.

10 Delusions of Guilt or Sin [_] 24
The patient believes that he has committed some terrible sin or done something unforgivable.

11 Grandiose Delusions [_] 25
The patient believes he has special powers or abilities.

0=None	1=Questionable	2=Mild	3=Moderate	4=Marked	5=Severe

12 Religious Delusions [_] 26
The patient is preoccupied with false beliefs of a religious nature.

13 Somatic Delusions [_] 27
The patient believes that somehow his body is diseased, abnormal, or changed.

14 Delusions of Reference [_] 28
The patient believes that insignificant remarks or events refer to him or have special meaning.

15 Delusions of Being Controlled [_] 29
The patient feels that his feelings or actions are controlled by some outside force.

16 Delusions of Mind Reading [_] 30
The patient feels that people can read his mind or know his thoughts.

17 Thought Broadcasting [_] 31
The patient believes that his thoughts are broadcast so that he himself or others can hear them.

18 Thought Insertion [_] 32
The patient believes that thoughts that are not his own have been inserted into his mind.

19 Thought Withdrawal [_] 33
The patient believes that thoughts have been taken away from his mind.

20 Global Rating of Delusions [_] 34
This rating should be based on the duration and persistence of the delusions and their effect on the patient's life.

3. BIZARRE BEHAVIOR

21 Clothing and Appearance [_] 35
The patient dresses in an unusual manner or does other strange things to alter his appearance.

22 Social and Sexual Behavior [_] 36
The patient may do things considered inappropriate according to usual social norms (e.g., masturbating in public).

23 Aggressive and Agitated Behavior [_] 37
The patient may behave in an aggressive, agitated manner, often impredictably.

0=None	1=Questionable	2=Mild	3=Moderate	4=Marked	5=Severe

24 Repetitive or Stereotyped Behavior [_] 38
The patient develops a set of repetitive actions or rituals that he must perform over and over.

25 Global Rating of Bizarre Behavior [_] 39
This rating should reflect the type of behavior and the extent to which it deviates from social norms.

4. POSITIVE FORMAL THOUGHT DISORDER

26 Derailment [_] 40
A pattern of speech in which ideas slip off track onto ideas obliquely related or unrelated.

27 Tangentiality [_] 41
The patient replies to a question in an oblique or irrelevant manner.

28 Incoherence [_] 42
A pattern of speech that is essentially incomprehensible at times.

29 Illogicality [_] 43
A pattern of speech in which conclusions are reached that do not follow logically.

30 Circumstantiality [_] 44
A pattern of speech that is very indirect and delayed in reaching its goal idea.

31 Pressure of Speech [_] 45
The patient's speech is rapid and difficult to interrupt; the amount of speech produced is greater than that considered normal.

32 Distractible Speech [_] 46
The patient is distracted by nearby stimuli which interrupt his flow of speech.

33 Changing [_] 47
A pattern of speech in which sounds rather than meaningful relationships govern word choice.

34 Global Rating of Positive Formal Thought Disorder [_] 48
This rating should reflect the frequency of abnormality and the extent to which this affects the patient's ability to communicate.

Groningen Social Disabilities Schedule-II

0= No disability 1= Some disability 2= Moderate disability
3= Severe disability 8= Insufficient information 9= Not applicable

1. Role of **self-care**
    A. Personal care -
    B. Self-presentation -
2. **Family** role
    A. Contribution to atmosphere and preservation -
    B. Contribution to the economic independence -
    C. One person household (only for individuals living alone) -
3. **Kinship** role: relationships with parents and siblings
    A. Affective relationship with parents -
    B. Actual contacts with parents -
    C. Affective relationship and actual contacts with siblings -
4. **Partner** role: relationship with partner in marriage or cohabitation
    A. Affective relationship -
    B. Sexual relationship -
    C. Active interest in establishing a relationship with a partner (only for single individuals with no steady partner) -
5. **Parental** role: relationship with children
    A. Affective relationship -
    B. Actual involvement -
6. **Citizen** role: interest and participation in sexual life
    A. General interest -
    B. Participation in societal groups, associations and/or clubs -
    C. Interests of fellow citizens -
7. **Social** role: relationships with friends and acquaintances
    A. Quality of contacts -
    B. Frequency and extent of contacts -
8. **Occupational** role: regular daily activities
    A. Daily routine -
    B. Work performance -
    C. Contacts with others -
    D. (other) daily activities -

SUMD (Abbreviated Version)

0: Not applicable; 1: Aware; 2: Somewhat aware; 3: Unaware

1) **Awareness of mental disorder:** In the most general terms, does the subject believe that he or she has a mental disorder?
2) **Awareness of the consequences of mental disorder:** What is the subject's belief regarding the reason(s) he or she has been unemployed, evicted, hospitalized, etc.?
3) **Awareness of the effects of drugs:** Does the subject believe that medications have diminished the severity of his or her symptoms (if applicable)?
4) **Awareness of hallucinatory experiences:** Does the subject believe that he or she experiences hallucinations as such? Rate his or her ability to interpret this experience as primarily hallucinatory.
5) **Awareness of delusional ideas:** Does the subject believe that he or she experiences delusions as such, that is, as internally produced erroneous beliefs ? Rate his or her awareness of the implausibility of the belief if applicable.
6) **Awareness of disorganized thoughts:** Does the subject believe that his or her communications are disorganized?
7) **Awareness of blunted affect:** >Rate the subject's awareness of his or her affect as communicated by his or her expressions, voice, gestures, etc. Do not rate his or her evaluation of his or her mood.
8) **Awareness of anhedonia:** Is the subject aware that his or her behaviour reflects an apparent decrease in experiencing pleasure while participating in activities normally associated with such feelings?
9) **Awareness of lack of sociality:** Is the subject aware that he or she shows no interest in social relationships?

Medication Adherence Rating Scale

Please respond to the following statements by circling the response which best describes your behaviour or the attitude you have held toward your medication in the past week.

1. Do you ever forget to take your medication? Yes / No
2. Are you careless at times about taking your medicine? Yes / No
3. When you feel better, do you sometimes stop taking your medicine? Yes / No
4. Sometimes if you feel worse when you take the medicine, do you stop taking it? Yes / No
5. I take my medication only when I am sick Yes / No
6. It is unnatural for my mind and body to be controlled by medication Yes / No
7. My thoughts are clearer on medication Yes / No
8. By staying on medication I can prevent getting sick Yes / No
9. I feel weird, like a “zombie”, on medication Yes / No
10. Medication makes me feel tired and sluggish Yes / No

The Global Assessment of Functioning (GAF)

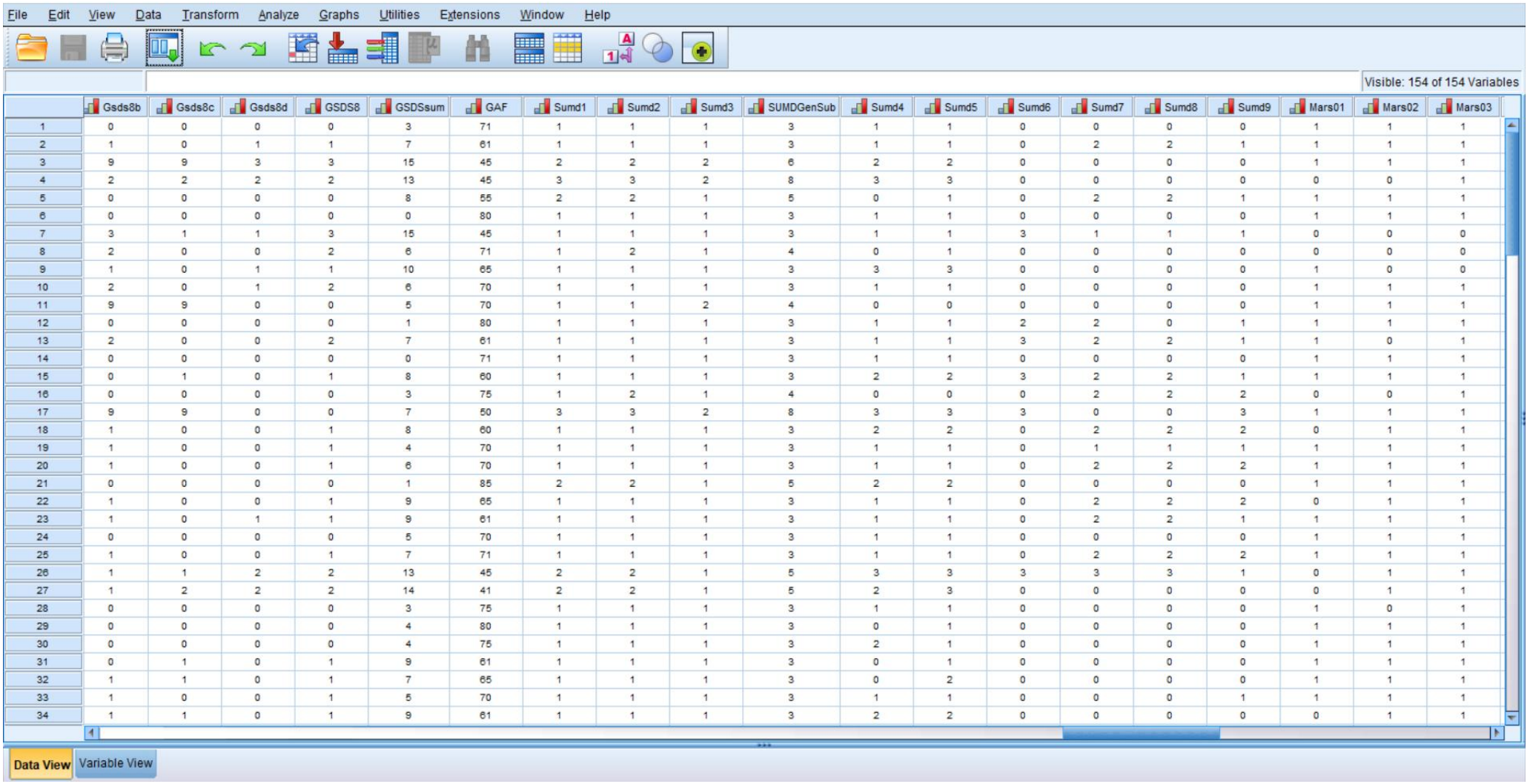
Source: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition

• **100-91:**	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
• **90-81:**	Absent minimal symptoms (e.g. mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., an occasional argument with family members).
• **80-71:**	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational, or school functioning (e.g., temporarily falling behind in school work).
• **70-61:**	Some mild symptoms (e.g., depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
• **60-51:**	Moderate symptoms (e.g., flat and circumstantial speech, occasional panic attacks) OR moderate difficulty in social occupational, or social functioning (e.g., few friends, conflicts with co-workers).
• **50-41:**	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).
• **40-31:**	Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work, child frequently beats up younger children, is defiant at home, and is failing at school).
• **30-21**	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day, no job, home, or friends).
• **20-11**	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute).
• **10-1**	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.
• **0**	Inadequate Information.

Global Assessment of Function – Cognition in Schizophrenia (GAF-CogS)	
100 ┆ 91	Superior cognitive functioning in a wide range of activities, is sought out to work on cognitively demanding problems, maintains superior level of functioning in a cognitively demanding vocation.
90 ┆ 81	Absent or minimal cognitive deficits (e.g., occasional lapses of memory or word finding difficulty), good functioning in all cognitive areas, effective functioning and engagement in cognitive tasks, no more than everyday concerns about cognitive performance.
80 ┆ 71	If cognitive deficits are present, they are transient and expectable reactions to stressors (e.g., difficulty concentrating after family argument), no more than slight impairment in social, occupational or school functioning due to cognitive deficits.
70 ┆ 61	Some mild cognitive symptoms (e.g., difficulty concentrating or memory lapses) OR some difficulty in social, occupational or school functioning due to cognitive problems (e.g., had to repeat a course in college due to cognitive problems).
60 ┆ 51	Moderate cognitive symptoms (e.g., persistent problems paying attention or forgetting of scheduled events) OR moderate difficulty in social, occupational or school functioning due to cognitive problems (e.g., had to take a leave of absence from school).
50 ┆ 41	Serious cognitive problems (e.g., continuous problems with attention, memory, or planning) OR any serious impairment in social, occupational or school functioning due to cognitive problems (e.g., family problems caused by deficits, unable to keep a job).
40 ┆ 31	Severe cognitive problems interfering with multiple social, occupational, or school functions (e.g., an individual is unable to work in competitive employment, has difficulty in supported employment, and has difficulty assisting with chores at residence).
30 ┆ 21	Cognitive deficits are so pronounced that they interfere with virtually all aspects of functioning, including meaningful communication and goal directed activity (e.g., difficulty sustaining conversation, performing basic activities of daily living).
20 ┆ 11	Some danger of harm to self or others due to cognitive deficits (gross impairments of planning/judgment, failure to recognize consequences of actions, frequently disoriented, wandering, or confused).
10 ┆ 1	Persistent danger of harm to self or others OR inability to maintain personal hygiene due to cognitive deficits (e.g., no meaningful communication, inability to perform even basic self care due to problems organizing behavior)
0	Inadequate information

The detailed Cognitive Assessment Interview (CAI) and the images used in the TRENDS tool cannot be shared here due to copyright issues.

SPSS Master Sheet: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Visible: 154 of 154 Variables

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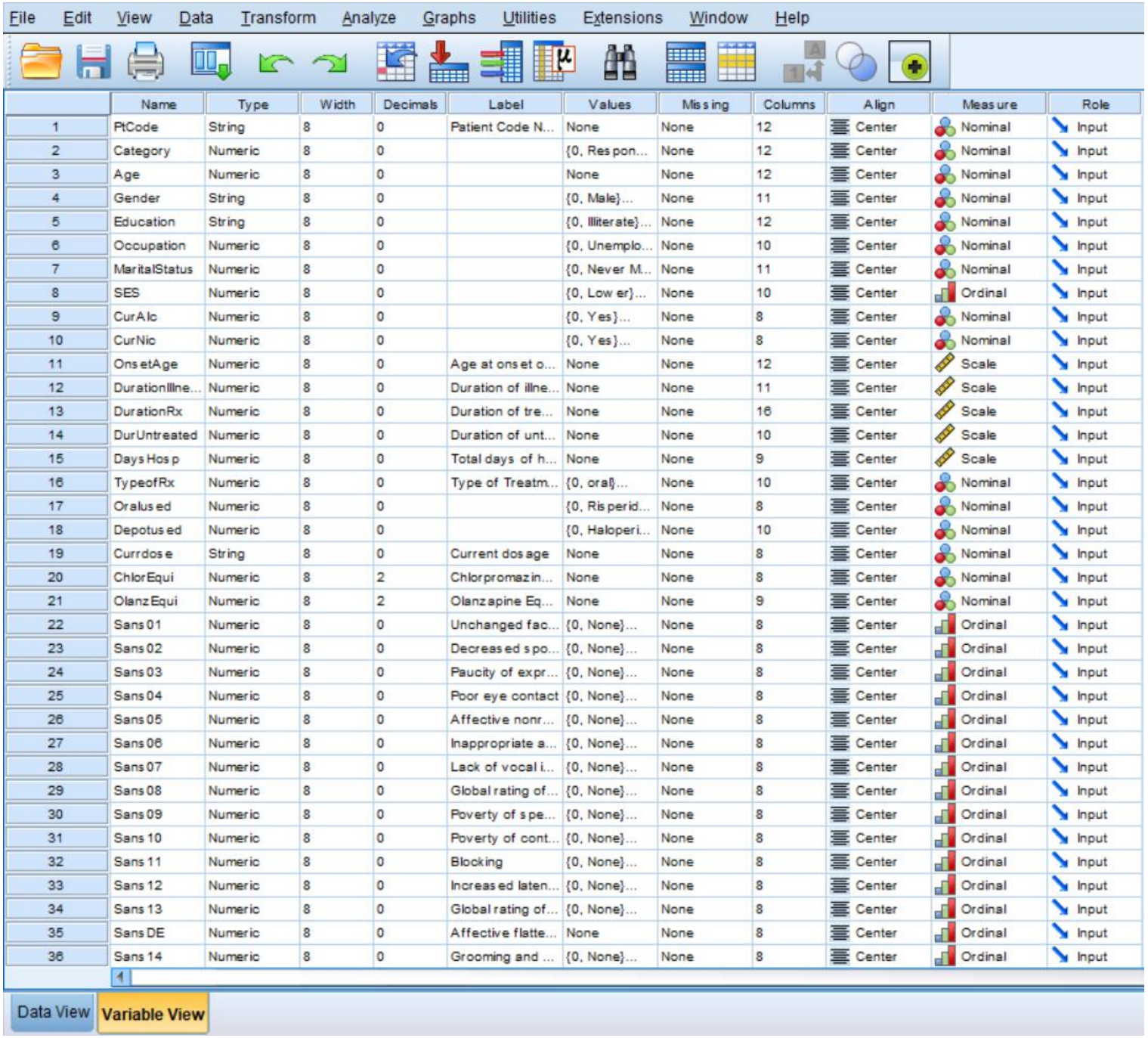
Data View Variable View



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25	Sans04	Numeric	8	0	Poor eye contact	{0, None}...	None	8	Center	Ordinal	Input
26	Sans05	Numeric	8	0	Affective nonr...	{0, None}...	None	8	Center	Ordinal	Input
27	Sans06	Numeric	8	0	Inappropriate a...	{0, None}...	None	8	Center	Ordinal	Input
28	Sans07	Numeric	8	0	Lack of vocal i...	{0, None}...	None	8	Center	Ordinal	Input
29	Sans08	Numeric	8	0	Global rating of...	{0, None}...	None	8	Center	Ordinal	Input
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Data View Variable View