Chapter 5.0
METHODS

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5.1 SETTING

The study was conducted at National Institute of Mental Health & Neuro Sciences (NIMHANS) in collaboration with S-VYASA Yoga University.

Ethical Clearance:

Study was approved by the Ethics Committee of both the institutions.

Eligible and willing subjects were explained about the nature of the trial including possible adverse effects in the language understandable to them. Subjects were explained about their equal chance in falling to either yoga therapy or waitlist control group. They were also explained about their right to withdraw from the trial at any point of time if they wished not to continue, without any impact on their regular treatment by the treating team. All the subjects were recruited with written informed consent.

Copy of informed consent and ethics committee approval letter is attached in the appendix.

5.2 STUDY DESIGN

Randomized controlled trial

5.3 SELECTION OF SUBJECTS

Inclusion criteria

1. Diagnosis of schizophrenia (DSM-5) (American Psychiatric Association, 2013b)
2. CGI-S Score $\geq$3 (Clinical Global Impression - Severity) (Guy W, 2000).Schizophrenia patients stabilized with antipsychotic medication for minimum 4-6 weeks.
3. Age range: 18-45years
4. Either sex
5. Written informed consent

Exclusion criteria

1. Features suggestive of risk of harm to self (example-suicidal risk) or others (example-aggression)

2. Need for Electroconvulsive therapy/given ECT in last three months.
3. Co-morbid substance dependence in the past 6 months or substance abuse in the past 1 month as per DSM 5, except nicotine.
4. Significant neurological disorder like seizure disorder, recent head injury, etc. evaluated by detailed neurologic examination.
5. Lifetime history of significant head injury
6. Pregnancy or postpartum (<6 weeks after delivery)

The demographic and clinical information (history of present illness as well as any other medical illness, family & personal history) regarding the patients was collected using structured proforma.

Diagnosis of schizophrenia was made as per DSM- 5 by a psychiatry resident and confirmed using Mini-International Neuro psychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) Psychopathology was assessed using structured assessment scales.

5.4 SAMPLE SIZE CALCULATION

Sample size was calculated based on the effect size (d=1.1) for the Facial Emotion Recognition task, from a previous study (Jayaram et al., 2013) .Sample size required to detect a significant difference in the variable of interest with a power of .80, allowing for 5% type I error, was 32 (16 in each arm). Considering the drop out of 16% in previous studies, sample size was rounded to 40 (20 in each arm)

5.5 SUBJECTS RECRUITMENT & RANDOMIZATION

Schizophrenia patients attending services at psychiatry department (outpatients=29; inpatients=11) of NIMHANS, were assessed for eligibility by a psychiatry resident and the diagnosis was confirmed using Mini-International Neuro Psychiatric Interview (MINI). With written informed consent, patients who were stabilized on antipsychotics for at least 6 weeks and were co-operative for yoga practices were recruited. Out of 478 screened subjects, 339 were eligible for study and 40 eligible subjects agreed for participation in the study. The data was collected from March 2016 to July 2017. Random assignment of

eligible and willing subjects to Yoga Therapy Group(YT) or Waitlist Control (WL) was done by the research scholar with Sequentially Numbered Opaque Sealed Envelope(SNOSE) method. Computer generated random numbers were used for treatment assignment. Random numbers were generated by a scientific officer who was not involved in assessment or recruitment of the subjects.

5.6 INTERVENTION

Yoga module validation

We began by reviewing the classical and contemporary yoga related texts to develop the content of the module. Texts on *Patanjali yoga sutras, Hatha yoga pradipika, Shiva samhita, Gerhanda samhita, Hatharatnavali, Bhagavad gita, Upanishads* and *Yoga vasistha* were reviewed (Iyengar BKS, 2007) (Muktibodhananda, 1998) (Pancham Singh & Rai Bahadur Srisa Chandra Vasu, 2009) (Mahadevan TMP, 2010)(Sri Janananda Bharati, 1982) (Chinmaya International Foundation, 2012).

Practices that could potentially target positive, negative, and cognitive symptoms as well as medication-related side-effects were searched from classical and contemporary literature. Although the practices included were based on traditional texts, these do not give exact symptom-based guidelines for practices; yoga is a science meant for achieving liberation and not for therapy. Hence the components of the module have been selected by approximating descriptions of mental and physical benefits of specific yoga practices with the symptom dimensions of schizophrenia. Practices which may be difficult to teach and practice for patients with schizophrenia and those that are contraindicated in common disorders like hypertension, cardiovascular diseases, etc. were excluded. Likewise, practices that pose difficulty to objectively verify, were not chosen. To suit the patients' needs, like use of wall support some practices were modified. The yoga module that was designed is composed of slow movements with breathing awareness, loosening exercises including *surya namaskara, asanas, pranayama, Om japa* and relaxation. The duration of the yoga module is approximately one hour.

Validation process

The designed yoga module was sent along with three case vignettes of adults with symptoms of schizophrenia to 30 Yoga experts, of whom 10 experts responded with their scores and comments. The experts rated the usefulness of the practices in the module on a scale of 1-5 (1- not at all useful; 2- little useful; 3- moderately useful; 4- very much useful; 5-extremely useful). Content Validity Ratio (CVR) for suitability of items and Intra Class Correlation (ICC) coefficient for inter rater reliability were calculated. Dichotomous (yes/no) and qualitative responses were also obtained from the experts to determine the appropriateness of duration of each yoga session and the whole yoga training programme. Details of the yoga module is given below (table-5.1) and discussed in detail in earlier publication (Govindaraj, Varambally, Sharma, & Gangadhar, 2016).

Validated Yoga module was administered (Subject performing yoga, Figure-5.1) to the Yoga group for 60 min, 4-5 sessions per week, with a total of 20 sessions to be completed within 6 weeks. Maximum 3 subjects were taught together in a session. Majority of the subjects finished 20 sessions in 6 weeks. Few subjects finished in 4 weeks. Waitlist participants were offered Yoga after 6 weeks.

Table-5.1 Yoga module

S.No	Practice	Duration
	Loosening Exercises	
1	Jogging	1min 45 sec
2	Mukha Dhouti	30 sec
3	Twisting	1 min
4	Hand stretch breathing	1 min
5	Forward & Backward bending	1 min
6	Tiger breathing	1 min
7	Sideward bending	1 min
8	Shashankasana breathing	1 min

9	Surya namaskar (12 rounds)	10-15min
	Yogasana	
1	Vakrasana	1 min
2	Ustrasana	1 min
3	Bhujangasana	1 min
4	Shalabhasana	1 min
5	Dhanurasana	1 min
6	Vipreetakarani	3 min
7	Matsyasana	1 min
	Pranayama	
1	Bhastrika	2.5 min
2	Nadishuddhi	3 min
	Chanting Meditation/Relaxation	
1	Nadhanusandhana(A,U,M & AUM Chanting)	10 min
2	Quick Relaxation Technique	4 min
	Total Duration	50-60 min

5.7 ASSESSMENTS

A trained yoga therapist gave the yoga intervention to subjects. A Psychiatry resident did the clinical assessments and was blind to the treatment allocation. Clinical assessments (positive symptoms, negative symptoms and social disability/functioning) which are subjective were assessed by a blind assessor (Psychiatry resident) and the social cognition assessment which is a computer based objective test (less prone to bias), was done by non-blinded research scholar.

Fig-5.1 Subject performing Yoga (with subject's consent)

All the assessments were done at the baseline and at the end of 20 sessions of Yoga training. Timeline and the details of assessment variables are as follows,

Table-5.2 Assessment details and timeline

S.no	Variables	Baseline	4th week/end of 20 sessions yoga
1	SOCRATIS	+	+
2	TRENDS	+	+
3	MNA-fNIRS	+	+
4	SANS & SAPS	+	+
5	GSDS-II	+	+
6	CGI	+	+
7	B-CATS	+	+

Intake Proforma

A structured proforma was used to collect the details of socio-demographic and clinical variables including age-at-onset, type of onset, and duration of illness

Mini-International Neuropsychiatric Interview (M.I.N.I.)

MINI is a short structured diagnostic interview for DSM-IV-TR and ICD-10 psychiatric disorders.

Social Cognition Rating Tool in Indian Setting (SOCRATIS)

SOCRATIS is a tool, which was validated, in the Indian socio-cultural context to assess social cognition in schizophrenia patients. It assesses theory of mind (first order, second order and faux pas), attribution styles (32 point questionnaire) and social perception [SoCueReTI -Social Cue Recognition Test-Indian setting].

Consistent with expert committee recommendations (Green et al., 2008) , we selected 4 out of the 5 recommended social cognition domains, namely, Theory of Mind (ToM), emotion processing, social perception, and attributional bias. ToM, social perception and attributional bias will be assessed using the Social Cognition Rating Tools in Indian Setting (SOCRATIS). Emotion processing will be assessed using the Tool for Recognition of Emotions in Neuropsychiatric DisorderS (TRENDS) (Rishikesh V Behere et al., 2008).

SOCRATIS and TRENDS have undergone cultural adaptation (e.g., use of native names, attire, and actors) and translational procedures (e.g., using conceptual, rather than literal, translations in two Indian languages) to modify the tasks to the Indian cultural setting, without disturbing the actual social cognition constructs that they were meant to test. The content validity, in terms of fidelity to the original construct and cultural appropriateness of these tasks has been found to be satisfactory. When tested on bilinguals, there was good concurrence of their performance in the original and the modified tasks (concurrent validity). These procedures and their validation have been described in further detail in previous studies.

To avoid learning effect, each domain in SOCRATIS was divided equally into two parts. One part was used at the baseline and the second part was used at the end of 20 sessions of Yoga training.

Theory of mind

Tasks included two each of 1st order [based on Sally-Anne (Wimmer & Perner, 1983) and Smarties tasks], 2nd order false belief picture stories [based on ice-cream van (Perner & Wimmer, 1985) and missing cookies (Stone, Baron-

Cohen, & Knight, 1998) tasks], two metaphor–irony stories [adapted from (Drury, Robinson, & Birchwood, 1998)] and ten faux pas recognition stories [based on the faux pas recognition test(Stone et al., 1998)]. These story-based tasks examine the ability at different complexity levels to 'meta-represent' mental states of others (e.g., Suresh thinks that Rani will go to the temple area to buy the ice-cream because she has not seen the ice-cream man go towards the school).

Following are the different ToM tasks used in SOCRATIS

Table-5.3 ToM Assessment tasks

Domain	Task
First order ToM	Shanti Ravi task & Sweet box task (modified from Sally-Anne task & smarties task)
Second order ToM	Ice-cream man task & Hidden bananas task (modified from ice-cream van task & Missing cookies task)
Metaphor-Irony	Metaphor-Irony stories (modified from Metaphor-Irony stories)
Faux pas	Faux pas recognition test (modified from Faux pas recognition test)

Attributional bias

This was assessed using a 32-point questionnaire where subjects were required to make causal attributions for positive and negative social events, adapted from the Internal, Personal, and Situational Attributions Questionnaire (Kinderman & Bentall, 1996)

Social perception

A set of 18 true/false questions were asked on social (e.g., Ali asked many questions about the movie because he was trying to impress Sunil) and non-social cues (e.g., Harish and Lakshmi were looking over a book together) after showing the subjects four each of low and high emotion videos depicting a social interaction. This test was adapted from the social cue recognition test (Corrigan & Green, 1993a).

As mentioned above, both SOCRATIS and TRENDS have been validated in the Indian cultural setting. Their psychometric properties (content, concurrent and known-groups validity, internal consistency and external validity) have been found to be satisfactory. Each test, except attributional bias, provides an index of the respective test performance, which is equivalent to the score of an individual on the test divided by the maximum score possible. We consider metaphor and irony detection as 1st and 2nd order ToM respectively. Faux pas recognition is often described as a higher order ToM ability (Brüne, 2005)

Tool for Recognition of Emotions in Neuropsychiatric DisorderS (TRENDS)

This is a tool validated for use in the Indian population (Rishikesh V Behere et al., 2008), which captures the full range and nature of emotional expressions akin to real life situations and can be utilized for behavioural and functional imaging studies in Indian patients. It takes into account variations of age and sex on emotional expressions and is a culture-sensitive tool. This is a culturally sensitive, ecologically valid tool, consisting of 52 static (still) and 28 dynamic (video clip) images (i.e. totally 80 images) of six basic emotions – happy, sad, fear, anger, surprise, disgust, and a neutral expression emoted by four experienced actors (one young man, one young woman, one older man, and one older woman).

Scale for Assessment of Negative Symptoms (SANS) & Scale for Assessment of Positive Symptoms SAPS: (Andreasen, 1984a) (Andreasen, 1984b)
The SANS is a 25-item scale designed to assess the negative symptom complex in five domains including alogia, affective flattening, avolition-apathy, anhedonia-asociality and attention. The SAPS is a 34-item scale designed to assess positive symptoms of schizophrenia in four domains of hallucinations, delusions, bizarre behavior and formal thought disorder. Ratings were done based on clinical interview, direct observation and any additional sources of information. The scale is on 0-5 spectrum (0=not present, 5=severe). It takes around 15-20 minutes to administer the scale

Groningen Social Disabilities Schedule (GSDS-II)

The Groningen Social Disabilities Schedule (Wiersma, DeJong, & Ormel, 1988), which is a semi-structured, culture-neutral interview, based on the WHO Disability Assessment Schedule-II was employed for assessment of socio-occupational functioning of patients.

Clinical Global Impression (CGI)

CGI-S (severity) was used at the baseline for assessing severity of the illness and CGI-I (Improvement) was used at the end of one month of intervention (Guy W, 2000).

Brief Cognitive Assessment Tool for Schizophrenia (B-CATS)

B-CATS comprises of three tasks i.e., Digit Symbol-Coding, Semantic Fluency, and Trail Making Test-B. Its reliability and Validity have been well established. It is easy to administer and takes less than 15 minutes to complete the assessment (Hurford, Marder, Keefe, Reise, & Bilder, 2011).

Clinical assessments (SANS, SAPS, GSDS & CGI) were done by psychiatry resident, who was blind to the treatment allocation. Social Cognition including MNA measured by fNIRS and neuropsychological tests (B-CATS) were done by the research scholar. Yoga Performance by the subjects were monitored by trained yoga therapist. Blinding of the research scholar was not possible as yoga was taught to the subjects by the research scholar. However, the social cognition assessment done by research scholar is a computer based objective test and is not prone to bias unlike the clinical scales.

Functional Near Infra-Red Spectroscopy (fNIRS) methods

Optical data was acquired with a continuous wave fNIRS system [2 wavelengths (760nm & 850nm), 8 sources, 4 detectors, sampling frequency 6.25-Hz) (NIRScout, NIRx Medical Technologies, LLC, CA, USA). Based on 10-20 system, the optodes were placed with the help of a tight-fitting cap in a band like configuration covering locations corresponding left ventral premotor cortex relevant for mirror neuron activity (Fig-5.2). The average distance between optodes was about 3cm. fNIRS data was acquired during the paradigm for mirror neuronal activation (paradigm details as described below).

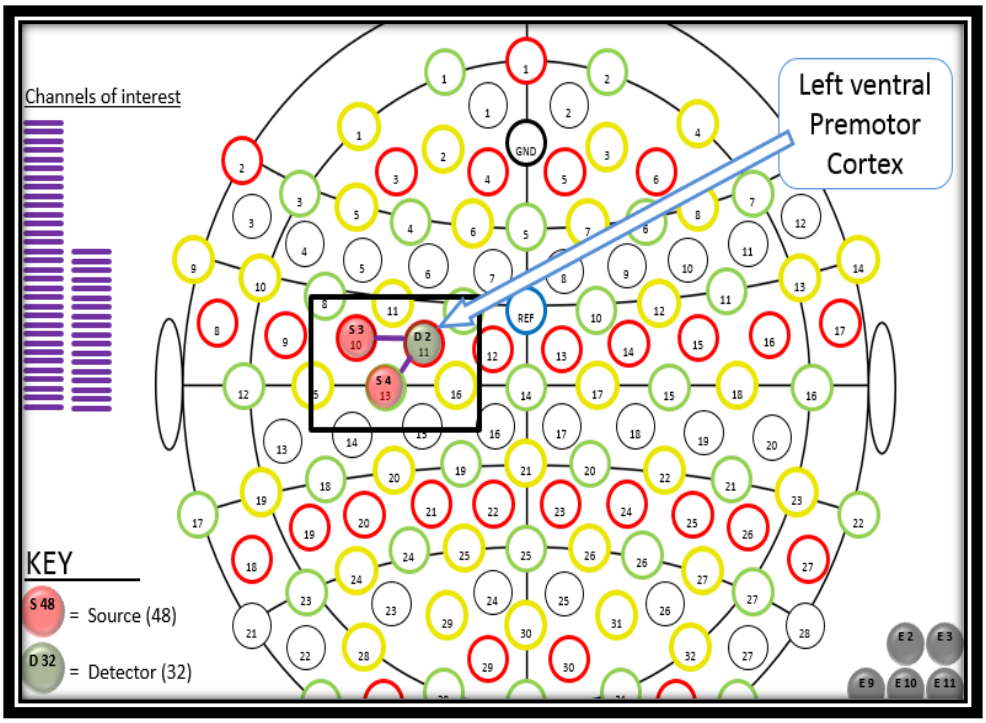

Figure-5.2 Probe Geometry for Left Ventral Premotor Cortex

Figure-5.3 Subject undergoing MNA task with fNIRS

Paradigm used for eliciting MNA is as follows,

After recording the baseline BOLD signal for 30 seconds, the subjects were given the following tasks while continuing the fNIRS experiment.

1. Static image/Resting state (60 seconds): The subjects were asked to observe a still image of a hand and a lock displayed on the monitor. See Fig-5.4

2a. Action observation (motor paradigm) (60 seconds): The subjects were asked to observe a video, which depicts the experimenter's hand, holding a key in lateral pinch grip (grasping objects between the side of the index finger and the thumb) to perform locking/unlocking actions. This action requires contraction of the FDI to abduct the index finger. See Fig-5.4

2b. Action observation (emotionally embedded motor paradigm) (90 seconds): In this condition, subjects were asked to observe a video of the emotionally embedded motor action that was developed in the earlier studies. An emotional context was shown in the video related to the action to be observed by the subjects (e.g., a person is desperately trying to open a jammed lock of a door to a room inside which someone is trapped). This action requires contraction of the FDI muscle of the person in the video to abduct the index finger while holding the key for unlocking. This paradigm was shown to give more consistent mirror neuron activation and has shown to enhance difference in MNA between healthy individuals and those with psychiatric disorders including schizophrenia (Bagewadi, Mehta, Thirthalli, & Gangadhar, 2014).

3. Action execution (60 seconds): Subjects were asked to execute the action of locking/unlocking with the hand holding a key in lateral pinch grip (grasping objects between the side of the index finger and the thumb)

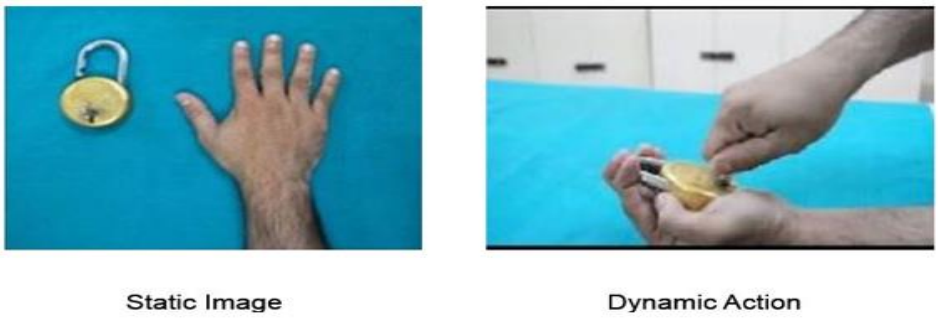

Fig-5.4 MNA paradigms

The sequence of displaying these experimental states to each subject were randomized. In order to guarantee optimal attention allocation during the fNIRS

experiments, subjects were instructed to pay attention to all the stimuli throughout the experiment.

Mirror neuron Activity was deduced by the difference in BOLD signal between a) action execution and resting state and b) action observation and resting state. An increment in BOLD (Blood Oxygen Level Dependant)-signal from premotor and motor cortices during action observation/execution relative to rest states was obtained a measure of putative MNA.