



## Suspend or amend? Randomized controlled trial on neuropsychological rehabilitation for epilepsy: A COVID-19 impact



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### ABSTRACT

COVID-19 caused devastating effects of human loss and suffering along with disruption in clinical research, forcing reconceptualization and modification of studies. This paper attempts to outline the steps followed and detail the modifications undertaken to deal with the impacts of the pandemic on the first ongoing randomized controlled trial on effectiveness of neuropsychological rehabilitation in adult patients with drug-resistant epilepsy in India. All modifications were based on evolving guidelines and circumstantial context and were planned, reviewed and approved by important stakeholders. Results obtained from the trial need to be interpreted and analysed within this context. These modifications have implications for wider outreach of neuropsychology services in India.

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### Introduction

Out of the 50 million people affected by epilepsy worldwide, 20–30% are refractory to medical treatment [1,2]. Neuropsychological impairment has been identified as being one of the most pronounced essential comorbidities in epilepsy [3–5]. Treatments for seizure control, such as surgery and antiseizure medication in polytherapy may exacerbate underlying cognitive deficits or even create new ones [5]. Therefore, there is clinical, conceptual and moral basis for the development and implementation of neuropsychological interventions [5], with numerous studies over the years lending support to its efficacy [6] and reiterating its importance [5].

**Abbreviations:** RCTS, Randomized Controlled Trials; TMT, Traditional Memory Training; LBT, Lumosity Brain Training; WHO, World Health Organization; BSWP, Biostatistics Working Party; INS, International Neuropsychological Society; ILAE, International League Against Epilepsy; NIH, National Institutes of Health; CTRI, Clinical Trials Registry of India; DRE, Drug Resistant Epilepsy; FGDs, Focus Group Discussions; TeleNP, Tele-Neuropsychology; HIPPA, Health Insurance Portability and Accountability Act.

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Randomized controlled trials (RCTs) are essential tools and are considered the gold standard for validating effective research hypotheses [7]. Two RCTs have been carried out for effectiveness of neuropsychological rehabilitation in adults with epilepsy. Engelberts et al. studied the efficacy of cognitive rehabilitation of divided attention in 50 patients with focal epilepsy who were treated with carbamazepine. They reported improved performance in retraining and compensatory groups compared to the control group. Neuropsychological assessment was completed before training, immediately after and again at 6 months. The compensation method was found to be more effective in improving self-reported cognitive abilities and quality of life (QoL) [8]. Thompson et al. in 2016 studied whether engagement in a memory training program and performing internet brain training exercises would improve memory function in patients with temporal lobe epilepsies (TLE). They assessed 77 patients, out of which 43% were post-surgical cases, who were randomized into 4 conditions. Traditional Memory Training (TMT) included compensatory methods including external aids and environmental adaptations. Lumosity Brain Training (LBT) included exercises for attention, speed, memory and problem solving. The other two conditions were a combination of TMT and LBT and no training. Results indicated a positive role for TMT in reducing the burden of memory impairment in TLE

with no conclusive evidence on the role of LBT [9]. However, the available literature is from resource rich settings which has limited direct evidence for applicability in lower income and literacy countries such as India [10].

The World Health Organization declared COVID-19 a pandemic on March 11, 2020 which led to dramatic changes in everyday life as well as clinical practice across the world [11,12]. Need for social distancing and quarantine forced extensive changes in healthcare with an inevitable shift to telehealth [13]. On 22nd March, 2020 Janta Curfew was declared in India and on the following day All India Institute of Medical Sciences (A.I.M.S), New Delhi, India suspended routine care in outpatient departments. One day after the first 14-day nationwide lockdown was imposed on 25th March, the All India Institute of Medical Sciences (A.I.M.S.), New Delhi, India, shifted to telehealth (i.e., telephonic consultation for all follow-up patients) [14]. By 25th June, 2020, along with the option of tele-consultation, walk in outpatient department services for follow-up patients were resumed [15] (Fig. 1).

Along with rapid changes in clinical practice, these extenuating circumstances also triggered unplanned changes in ongoing research and clinical trials [16]. As acknowledged by the Biostatistics Working Party, the COVID-19 pandemic is bound to have an impact on data collection, analysis and interpretation of clinical trial data. However, with patient safety being at the heart of every decision, there is also an ethical mandate to proceed with ongoing trials so that efforts undertaken by study participants, physicians and researchers can inform patient care [17].

Evidence suggests that trial modifications can introduce biases and raise doubts regarding the validity of the conclusions [18]. Some clinical and research speciality societies such as those of oncology, hepatology, cardiovascular disease and heart failure provided guidelines early on for conducting clinical trials during the pandemic [19–21]. The International Neuropsychological Society routinely updated guidelines and best practices through webinars and resource material [22,23].

The paper attempts to outline the steps followed and detail the modifications undertaken to deal with the impacts of the COVID-19 pandemic on the ongoing trial.

## Methods

### Pre COVID-19

The study was planned as an open label randomized controlled trial with parallel design for epilepsy rehabilitation. Neuropsychological outcome measures for the study were chosen based on domain and test recommendations by the International League Against Epilepsy and National Institutes of Health, USA [24,25]. Availability of corresponding Indian norms as well as access in the public domain were considered as important criteria for choosing the neuropsychological assessment profile (Table 1). All consenting patients were enrolled. Enrolled patients were randomized using computer generated lists to intervention and control groups. Sealed opaque envelopes were used for allocation concealment [26]. CONSORT guidelines were followed in the formation of the research design [27]. The study was approved by Institute Ethics Committee (IECPG-380/30.08.2018, RT-3/18.10.2018) and registered prospectively on Clinical Trials Registry of India (CTRI/2019/10/021777).

Once included as per the planned protocol of the study, the patients underwent baseline neuropsychological assessment (T1). The next assessments were planned immediately following the neuropsychological intervention (2 months after study inclusion [T2]). The 3rd assessment was planned at 3 months (maximum 5 months after study inclusion [T3]).

From December 2019 to March 2020, eligible patients with drug-resistant (focal) epilepsy (DRE) categorized as ‘post-surgical’ and ‘not cleared for surgery’ (after multidisciplinary case conference) from Department of Neurology at A.I.I.M.S, were referred for neuropsychology outpatient services. Comprehensive history was taken and checked to include: (a) drug-resistant epilepsy [28,29] (b) diagnosis made in the last 1.5–2 years (c) age from 18 to 45 years (d) males & females (e) fluent in Hindi, English or both, (d) handedness as right or left (e) if surgical, surgical approach of resection for temporal or extratemporal epilepsy at least 3 months following surgery [30] (f) primary caregiver with capacity and willingness to carry out home based activities (g) capacity and

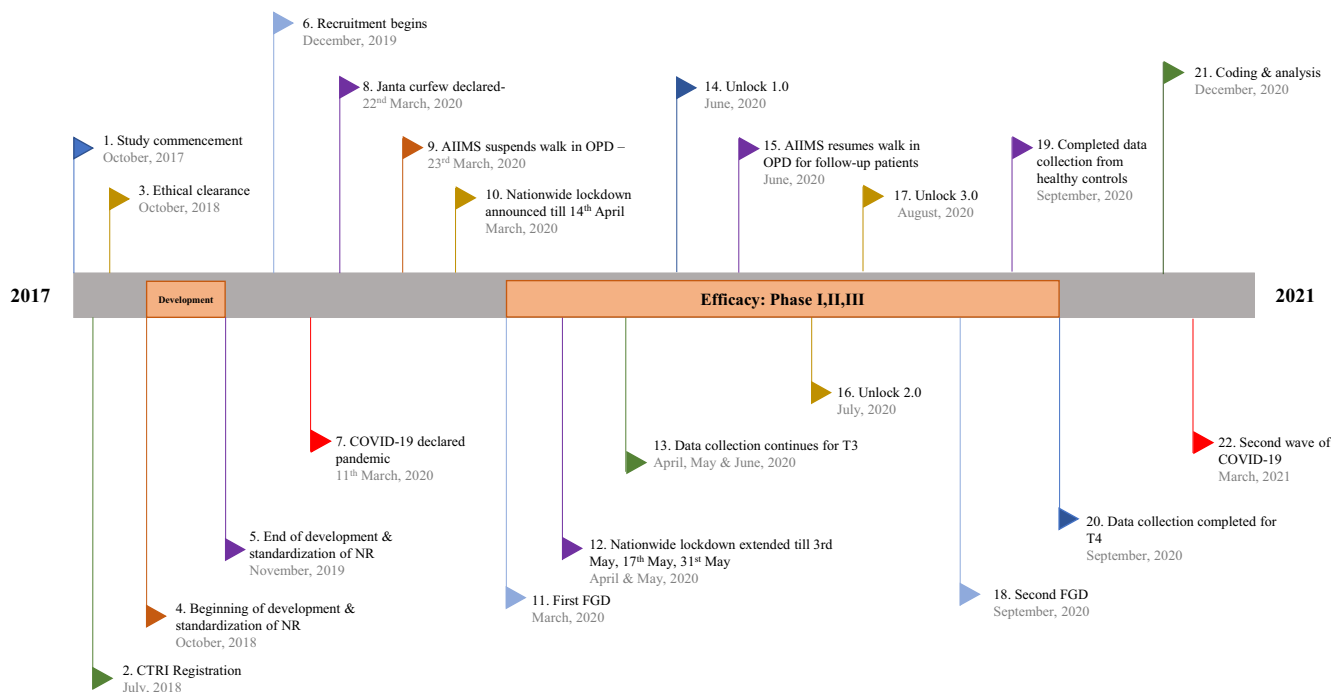


Fig. 1. Study schema.

**Table 1**  
Comparison of original and modified neuropsychological assessment protocol.

	Cognitive Domain	Original Protocol (Baseline, 2 month & 5 month follow-up)	Modified Protocol (5 month Follow-up)	Modified Protocol (6-7 month Follow-up)	Reference of Tele (video) assessment [22]
Screening	Intelligence	Standard Progressive Matrices	Not Required	Not Required	-
Primary Outcomes	Verbal Memory	Auditory Verbal Learning Test	-	Permission Taken	Video based
	Visual Memory	Complex Figure Test	-	Permission Denied & Not Feasible	-
	Everyday Memory	Everyday Memory Questionnaire	Everyday Memory Questionnaire	Everyday Memory Questionnaire	Video based
	Attention	Colour Trails Test	-	Permission Denied & Not Feasible	-
	Quality of Life	Quality of Life in Epilepsy-31	Quality of Life in Epilepsy-31	Quality of Life in Epilepsy-31	-
Secondary Outcome	Anxiety & Depression	Hamilton Anxiety Inventory, Hamilton Depression Inventory	Hamilton Anxiety Inventory, Hamilton Depression Inventory	Hamilton Anxiety Inventory, Hamilton Depression Inventory	Video based
	Caregiver Burden	Zarit Burden Interview	Dropped	Dropped	-

willingness to consent (h) > 15 PR on any subdomain of objective attention or memory [31]. Exclusion criteria were (a)  $IQ \leq 80$  [8] (b) any significant progressive disorders or unstable medical conditions requiring acute intervention [29] and (c) hourly seizures.

Aside from considering factors of motivation, consent, IQ and social support, in line with previous studies on neuropsychological rehabilitation in epilepsy, patients with impairment in the domain of interest were included [8,9]. Moreover, the economic feasibility aspect of rehabilitation potential was addressed as appointments for assessment and face-to-face session were coordinated with the patients follow-ups with their treating neurologist or neurosurgeon. Additionally, all the rehabilitation material was handed over to the patient and weekly telephonic follow-ups were planned to ensure the patient and caregiver do not need to travel to the tertiary care center.

We developed and standardized a 6-week, home based, caregiver assisted neuropsychological rehabilitation program for adult patients with DRE [32]. This includes culturally suitable and readable graphic psychoeducational material on (a) neuropsychological consequences of epilepsy [33] and (b) compensatory training using internal and external aids as well as (c) progressively difficult paper and pencil tasks of visual attention, verbal memory and visual memory for cognitive retraining [34-37]. A weekly telephonic follow-up, compliance assessment and feedback were planned [9].

Lockdown due to COVID-19 was declared at a point at which all baseline assessments (T1) and majority of home based rehabilitations were complete. Some T2 assessments were complete, while some T2 and all T3 assessments were pending (Fig. 2).

*Post COVID-19*

A committee of stakeholders (1 statistician, 2 epileptologists and 2 neuropsychologists working with PWE) was formed to meet routinely for focus group discussions to review progress, troubleshoot and determine the best solutions to follow [17]. This was achieved through 2 focus group discussions and 3 phases. For every phase, SS identified potential barriers and outlined probable evidence based solutions which were deliberated along with new recommendations given by stakeholders. These served as questions for discussion. All deliberations were strongly rooted in points to consider on implications of COVID-19 on methodological aspects of ongoing trials, safety of study participants, feasibility, limitations of the current government funded tertiary centre and

the socio-economic background of the patients visiting the hospital [17]. Discussion notes were logged by the investigators and another neuropsychologist. The following section outlines the deliberation themes through the 3 phases (Figs. 1 and 2):

*Phase I*

The most pressing concern was regarding the continuity of the ongoing study. During the first FGD we were in the first lockdown, financial support from the source of funding was continuing and there was grave uncertainty regarding the next few months. At the time of discussion, limited evidence existed regarding patients with epilepsy being at higher risk for COVID-19 [38]. With the first follow-up (T2) coming up, the patients were unable to travel to the hospital due to the lockdown and there were no existing guidelines for tele-neuropsychology (TeleNP) during COVID-19. Thus, T2 was dropped and the possibility of continuing with data collection by administering the subjective scales (i.e, questionnaires) from the original assessment protocol at T3 with assessment of COVID-19 related factors was deliberated upon (Fig. 2). A suggestion was made to drop caregiver burden scale (due to the presence of confounding factors) and provide elementary tele-support on factors related to COVID-19.

Based on the literature available, a proforma was designed to collect information on COVID-19 specific factors on domains of (a) exposure (b) residence (c) education & employment (d) personal & social life (e) general health (f) awareness & appointments and (g) epilepsy related factors [39,40]. In addition to others, a question on concern vis-à-vis each domain on a 5-point Likert scale (1-not at all concerned, 2-slightly concerned, 3-somewhat concerned, 4-moderately concerned, 5-extremely concerned) was also included. Most questions were designed in a way to gather descriptive data to be interpreted in frequencies or percentages later.

Additionally, a set of strategies were prepared for COVID-19 related concerns to offer instant tele-support. This included (a) information about availability of neurology tele-consultation at the hospital, (b) guidance in formulating questions to seek guidance from the treating consultant regarding epilepsy and COVID-19 (c) education on importance of medication adherence and maintaining proper sleep routine, (d) significance of reliable sources of information and limited exposure to news, (e) emphasis on physical rather than social distancing, (f) suggestion on forming study or work buddies to help adapt to or seek support for the virtual format and (g) if desired, appointment for memory rehabilitation [38,41].

**Open Label RCT with Parallel Study Design [CTRI/2019/10/021777]**

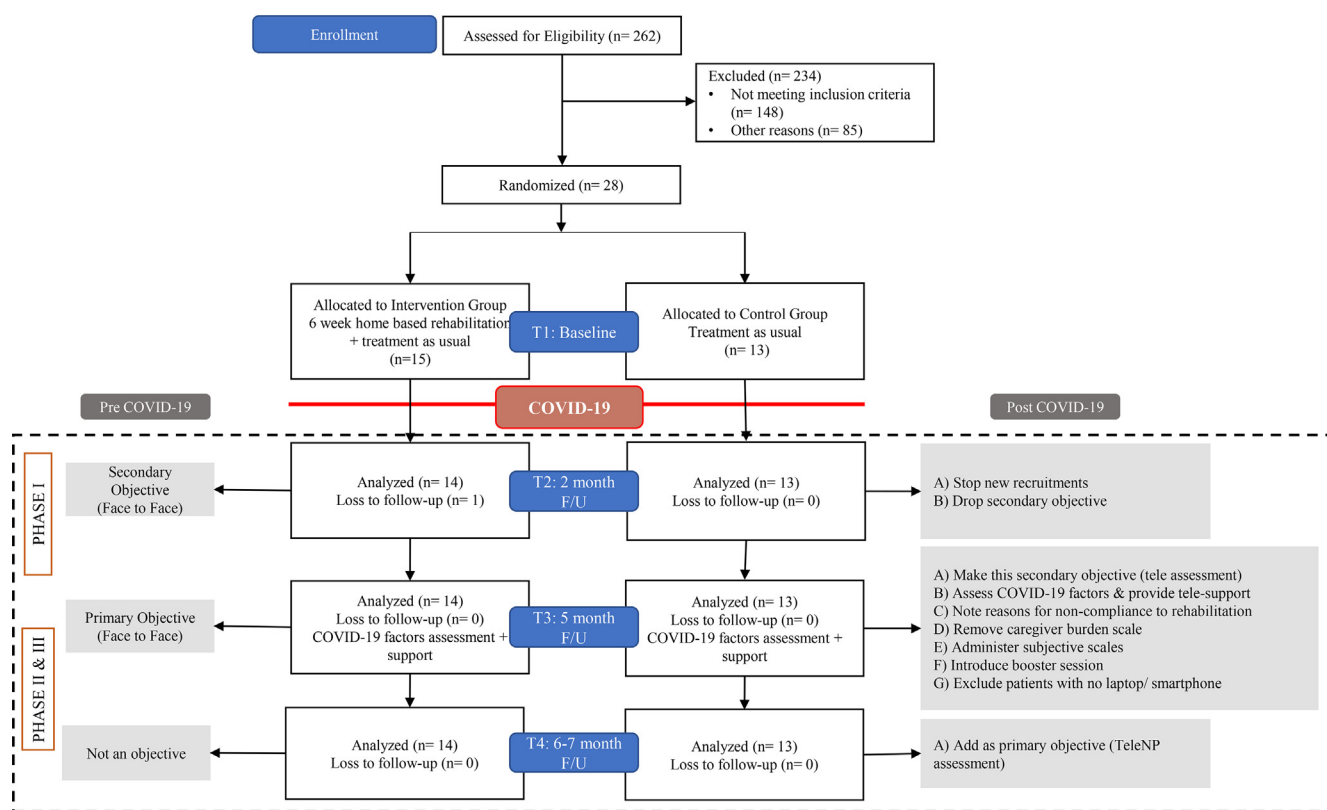


Fig. 2. CONSORT flow chart.

**Phase 2 & 3**

The months between the two focus group discussions saw a rapid surge in emerging guidelines and directives on trial modifications [17] as well as in the fields of TeleNP [42] and epilepsy [43]. Though the latter two were predominantly for clinical practice, potential solutions were considered by extrapolating these to clinical research [44].

Careful consideration of the available models of TeleNP, namely, clinic TeleNP, home-based TeleNP and hybrid TeleNP [23] resulted in the conclusion that home TeleNP would be most appropriate and feasible for the current study. However, no specific guidelines or review were available for TeleNP assessment in India. Thorough focused review of existing validation studies on the comparability of face-to-face and TeleNP assessments was carried out to find support for administration of outcome measures from the original assessment protocol [22]. A short telephonic survey with the patients on availability of smartphone and laptop revealed that though 78% had a laptop at home, for 11% of the patients the laptop was owned by a family member who was either a student or employed. Hence posing a barrier for its availability for tele-session during working hours. Furthermore, 30% revealed they had limited familiarity with a laptop. Nonetheless, 100% of the patients reported access to and familiarity with a smartphone. Thus, considering the socio-economic background of the patients, the option to use platforms that were Health Insurance Portability and Accountability Act (HIPAA) compliant through smart phones [23] was contemplated and approved. As a standard screen size would not be maintained for all patients, a decision was made to drop all outcome measures with visual stimuli (Table 1). Tests that required material manipulation were also dropped. Despite available support for tele-administration of list learning tests

[22], permission to use the Indian adaptation of the verbal list learning test (Auditory Verbal Learning Test) from NIMHANS battery [31] from the original assessment protocol was denied. The institute was in discussion with the original authors to convert the entire battery to online format. In the meanwhile, we reached out to original author of the Indian version of AVLT (sub test from the battery) and got necessary approval. The next step included pondering over the statistical and psychometric solutions to ensure validity of data collected from tele administration which is the backbone of neuropsychological assessment [24]. It was reiterated that since a consistent mode of assessment at both time points was being followed for all patients (that is, face-to-face at baseline and TeleNP at follow up), the nature of error in the data would be random as opposed to systematic. Furthermore, in line with the guidance to prioritize primary outcomes and modify protocols to facilitate data collection that can be adjudicated as surrogate for the primary outcome [45], it was recommended that data be collected from 20 healthy controls (who are not caregivers of patients in the ongoing trial) on AVLT through tele assessment. This data would be compared with the existing norms available from face-to-face assessment for comparability. In case norms from both groups are found to be statistically non-comparable, appropriate statistical adjustments could be made during analysis.

As required permissions and updated consent forms were pending for T3, major methodological changes were weighed again. While the original time points of assessment were planned based on available literature, one RCT on neuropsychological rehabilitation of attention in epilepsy did show sustained effects of rehabilitation at 6 months, hence supporting a longer follow-up [8]. This resulted in adding a new primary objective of follow-up assessment at 6-7 months (T4). Due to the possibility

of non-compliance to rehabilitation due to COVID-19, the prospect of including a semi structured interview to note reasons for non-adherence was discussed and finalized. This was planned to be used with a 5 point Likert scale of frequency of engaging in the strategies taught (never-every time). As the long term follow-up assessment period had to be extended to 6 months, introducing a booster rehabilitation session [46] was also reviewed and approved.

Before phase 3, a feasibility study was carried out to determine potential barriers to TeleNP assessment. This was completed on 10 adult patients with DRE from the neuropsychology outpatient services who were not a part of the ongoing trial. Findings from the feasibility study revealed the following barriers:

1. Downloading the HIPAA compliant platform minutes before the session and hence joining the virtual visit late as a result.
2. Audio concerns surfacing upon joining the visit. For example, taking a long time to connect with audio, or being unable to unmute.
3. Perceived importance of joining the session such as joining 15 minutes late despite reminders and dressing in inappropriate attire.
4. Poor internet connection and transmission lag time.
5. Session interruption by incoming calls on a cellular or smartphone after the session has been joined.
6. Distractions that interfere with assessment (i.e., loud noises such as a television in the background, presence of multiple family members asking questions, family member talking on the phone in the same room, or door bells and alarms).
7. Time taken to break for refreshments and time to set up the phone video at an appropriate angle during the session.

In order to combat the barriers identified as a result of the feasibility study, empirical solutions such as manual for preparedness of TeleNP session [47,48] to be shared with and explained to the caregiver and coding for validity of TeleNP assessment [49] were

concluded and developed. Based on the remote administration guide of Addenbrooke's Cognitive Examination-III, manual for preparedness included instructions on what needs to be ensured before and during the session. Instructions to be shared were written in simple language (Hindi and English) and explained beforehand to the caregiver over the phone. It was reiterated that the virtual session was a substitute for a face-to-face session and should be treated with the same level of importance as a scheduled hospital visit. Clear directive was shared on being ready with the HIPAA complaint platform preferably after testing with family or friends at least one hour before the scheduled session. This should also include ensuring the set-up is distraction free, the phone has been placed on a hard surface, the camera angle is correct and that the patient has their hands free. Furthermore, a suggestion for patients who would be using Wi-Fi to put the smartphone on airplane mode to avoid interruption by incoming calls was included. Depending on the feasibility, a recommendation was made to try to limit the Wi-Fi usage in the house by others during the session.

*Statistical analysis*

Statistical analysis was performed using STATA 14.0. Descriptive statistics of the demographic characteristics of the RCT and healthy control group was computed. Mann-Whitney U test was used to determine group differences on the demographic characteristics. Independent samples t-test using summary information was computed to compare the original norms with the data collected from healthy controls through tele-assessment.

**Results**

*Data collection from healthy controls*

Demographic characteristics of the RCT and healthy control groups were statistically comparable (Fig. 3). The original norms

	RCT Patients (N=28)	Healthy Controls (N=20)	P Value
Age (in years) (Mean ± SD)	27.08 ± 8.24	30.5 ± 8.19	0.160
Education (in years) (Mean ± SD)	13.64 ± 2.39	13.1 ± 3.31	0.514
Gender (Males/Females)	17/11	12/8	0.279

Comparison of demographics between RCT patients and healthy controls

	Learning		Immediate Recall		Delayed Recall		Long Term Retention		Recognition	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Exiting	55.68±6.53	61.90±7.06	12.42±1.95	13.50±1.76	12.48±1.98	13.67±1.86	94.45±12.30	96.03±10.17	14.61±0.76	14.70±1.32
Present (n=20)	59±7.30		12.9±1.85		12.6±1.85		95.9±6.48		14.3±0.67	
P Value	0.096	0.083	0.385	0.134	0.834	0.059	0.630	0.958	0.143	0.217

Comparison of AVLT norms collected through tele-administration with original norms (16-30 years college educated, males & females separately)

Fig. 3. Comparison of AVLT norms collected through tele-assessment with original norms.



**Table 2**  
COVID-19 related factors. This table was computed using Fisher's Exact Test/Chi-Square.

	Intervention Group Yes/No (%)	Control Group Yes/No (%)	P-value
<i>Exposure</i>			
Direct Contact	0/100	0/100	–
Presence of Symptoms	0/100	8/92	0.481
Positive Test	0/100	0/100	–
Time spent on COVID-19 News [Mean ± SD Median (Min, Max)]	15.71 ± 8.73 17.5 (5,30)	14.091 ± 8.8915 (5,30)	0.435 <sup>a</sup>
Overall concern Due to COVID-19* (1/2/3/4/5)	0/21/43/29/7	0/8/54/38/0	0.757
<i>Residence</i>			
Stuck during lockdown	0/100	0/100	–
Declared containment zone	7/93	15/85	0.596
Number of positive cases in society/area of residence [Mean ± SD Median (Min, Max)]	1.85 ± 3.99 0 (0,15)	7.3 ± 10.16 2.5 (0,28)	0.152 <sup>a</sup>
Overall concern about living status* (1/2/3/4/5)	36/50/7/7/0	23/38/23/8/8	0.713
<i>Education &amp; Employment</i>			
Pre-COVID-19 enrolment	72/28	69/31	0.568
Discontinuation	0/100	0/100	–
Increase house responsibilities	57/43	30/70	0.252
Difficulty adjusting to virtual format	70/30 (n = 10)	50/40 (n = 9)	
Overall concern due to work/study* (1/2/3/4/5)	28/0/36/36/0	15/23/38/15/8	0.298
<i>Personal &amp; Social</i>			
Financial Security	100/0	100/0	–
Increase in verbal/physical fights	20/80	23/77	1.00
Perceived social support	85/15	69/31	0.678
Overall concern for personal/social life* (1/2/3/4/5)	0/50/29/7/14	0/62/15/23/0	0.402
<i>General Health</i>			
Effect on routine	28/72	46/54	1.00
Problem with medication procurement	0/100	0/100	–
Other medical concerns	7/93	0/100	1.00
Overall concern about general health and wellbeing* (1/2/3/4/5)	0/21/43/36/0	0/46/38/16/0	0.310
<i>Awareness &amp; Appointments</i>			
Knowledge of tele-consultation	57/43	46/54	0.863
Missed routine follow-up due to COVID-19 lockdown	60/40	46/54	0.842
Overall concern about appointment* (1/2/3/4/5)	21/29/7/36/7	15/15/24/46	0.696
<i>Epilepsy</i>			
Perceived high risk for COVID-19	29/71	39/61	0.695
Increased seizure frequency	0/100	15/85	0.222
Cognitive status deterioration** (1/2/3/4/5)	7/14/43/36/0	0/46/46/8/0	0.109
Overall concern about epilepsy * (1/2/3/4/5)	0/0/50/43/7	0/8/30/54/8	0.704

<sup>a</sup>Mann Whitney U test; \*1: not at all concerned, 2: slightly concerned, 3: somewhat concerned, 4: moderately concerned, 5: extremely concerned; \*\* 1: much worse, 2: somewhat worse, 3: about the same, 4: somewhat better, 5: much better.

of face-to-face administration [31] and norms collected through TeleNP assessment were found to be statistically comparable on all domains of AVLT, namely learning (Males: p = 0.084; Females: p = 0.163), immediate recall (Males: p = 0.353; Females: p = 0.238), delayed recall (Males: p = 0.709; Females: p = .060), long term retention (Males: p = 0.617; Females: p = 0.968) and recognition (Males: p = 0.121; Females: p = 0.205). Due to the nature of original norms, separate computations were made for males and females. As the RCT group had age 27.4 ± 8.3 years and education 13.8 ± 2.3 years, data from the healthy controls was compared with available norms of 16–30 years, college educated (12 years plus) males and females.

*Assessment of COVID-19 related factors*

The intervention group (IG) and the control group (CG) were compared on factors related to COVID-19 (computed using chi-square/Fisher's exact test and Mann-Whitney U test in Table 2). None of the patients tested positive for COVID-19 at the time of data collection. 7% of the patients in the IG and 15% in the CG were

living in societies that had been declared containment zones. Majority of the patients (72% in the IG and 69% in the CG) were enrolled in either college or work before the onset of the pandemic and the pandemic did not impact their educational and employment status. Increase in household responsibilities and difficulty adjusting to the virtual format was reported by 57% and 70% of the patients in the IG and 30% and 50% of the patients in the CG respectively. All patients reported having financial security and no problem with procurement of medicines with only 7% of patients in the IG reporting facing other medical issues during the COVID-19 lockdown. Perceived social support was high in both the IG (85%) and CG (69%) However, a high level of concern was expressed regarding follow-up appointments with their treating neurologist by both the groups with 57% of the patients in the IG and 46% patients in the CG reporting missing follow up appointments due to the lockdown. Coming to epilepsy related factors, though both the groups were statistically comparable, 29% of the patients in the IG and 39% of patients in the CG perceived themselves as being high risk for COVID-19. Only 15% of patients in the CG reported increased seizure frequency after lockdown.

Furthermore, cognitive status deterioration since lockdown was reported by 21% and 46% of the patients in the IG and CG respectively.

**Non-compliance**

All patients completed 6 weeks of retraining tasks. Noncompliance was reported for using the taught strategies in everyday life. Out of the 14 patients in the IG, 0%, 7%, 57%, 22% and 14% reported their frequency to engage in the strategies as never, almost never, sometimes, almost every time and every time respectively. Themes of ‘increase in household responsibilities’, ‘distraction and stress due to ongoing pandemic’, ‘non availability of time due to increased workload of online classes/work from home’ and lastly, ‘increase in verbal/physical fights at home’ were identified as reasons for non-compliance to the rehabilitation activities. Examples and excerpts are detailed in Fig. 4.

**Discussion**

COVID-19 caused devastating effects of human loss and suffering along with disruption in clinical research, forcing reconceptualization and modification of studies [12]. The status of all research activities at A.I.I.M.S, in New Delhi, India was determined by the investigators and responsible parties on a case by case basis [16,17].

The decision to continue with data collection through TeleNP [17] posed challenges as TeleNP is a relatively underdeveloped field in India potentially impacted by limited resources, practice modifications, and a break from traditional style [50]. There is ample evidence for the use of computers and laptops as a mode for TeleNP assessment, however, the use of smartphones is yet not validated and has been explored in limited number of studies (see Park et al. 2017) [51]. In the present study, this was seen as a viable means of bridging the technological divide. Recent guidelines now see this as a necessary option to provide the underserved populations access to services during the pandemic [52].

Further, TeleNP raises its own concerns regarding the validity and accuracy of obtained test results. These include unanticipated distractions, patient characteristics as well as availability and expertise in technology. Additionally, in India, we are currently missing counter balanced cross over studies for comparison of face-to-face and TeleNP assessments with the international validation literature having underrepresented ethnic and non-English speaking minorities [52]. This unique challenge demanded creative solutions which are inherent to scientific enterprise. The decision to collect auxiliary data in the form of virtual assessment of healthy controls for comparison with existing normative data collected during face-to-face encounters revealed comparability which is relevant for data interpretation and analysis.

It is important and significant to note that there was limited exposure to COVID-19 in both groups and none of the patients had tested positive for COVID-19 at the time of data collection in the first wave. These results could have been significantly different in the deadly second wave which began in March 2021 resulting in suspension of outpatient department services again in April 2021 [53].

Furthermore, both groups were found to be comparable on COVID-19 related factors. As reported by Pandit and Agarwal [54], patients in the present study also reported difficulty in adjusting to the virtual format of health care delivery. However, none lost their jobs or discontinued the study due to the pandemic. Unlike the study by Sureka et al. [55] of predominantly male, rural patients from Rajasthan, India, all patients reported financial security and no difficulty with procurement of medicines. This could partly attributed to the socio-demographic background of the patients in the study [57% from rural India with 49% of the sample with a monthly income of less than 2390 Indian rupees (approximately 32 U.S. dollars)]. Concern regarding appointment and ability to reach healthcare provider were also reported by Miller and colleagues [56]. An interesting finding was the perception of social support by 85% and 69% of the patients in the IG and CG respectively. This along with factors of general health, finances and epilepsy related to COVID could have contributed to majority of the

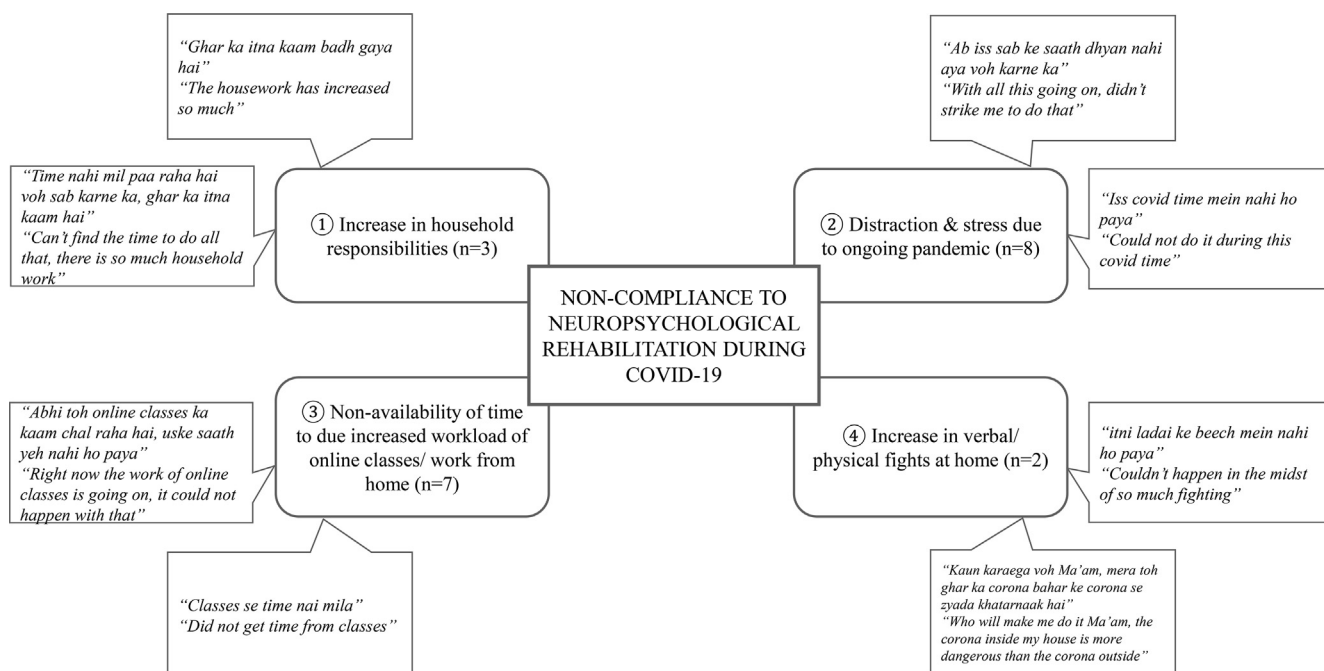


Fig. 4. Themes of noncompliance to rehabilitation strategies during COVID-19.

patients (overall 48%) being “somewhat concerned” regarding COVID-19.

Themes for non-compliance to rehabilitation during COVID-19 such as concerns about time commitment, lack of social support at home, duration of treatment and motivation are supported by literature in the context of compliance to drug regimen and home based exercises [57,58]. Moreover, recent studies from India as a collectivistic society, have highlighted increased domestic violence [59], difficulty in adjustment to work/study from home [54] as well as increase in unpaid household responsibilities due to unavailability of domestic workers [60] in the lockdown due to COVID-19. It is well acknowledged in neuropsychology literature that testing is just one component of neuropsychological assessment with collateral interviews and data supplementing data collected from standardized testing [24,61]. In the present study, reasons for non-compliance the intervention and an understanding of factors related to COVID-19 need to be woven into interpretation of outcome measures in future publications.

### Implications and future directions

Learnings from the adaptation process in a low resource country can serve the broader community of neuropsychology facing similar challenges. Though these would be culture sensitive, a timely feasibility study on the access and familiarity with technology can inform decisions on mode of assessment, outcome measures to include and update instructions for remote testing. Collecting context-specific supplemental data would help ensure accurate interpretation of the final results and serve as an innovating means to develop and collect norms to ensure continued best clinical and research practices.

Moreover, building on these modifications in India may help determine guidelines to follow for TeleNP (assessment and rehabilitation) with the shift to telehealth in the post-COVID-19 world. Additionally, this could help ensure a wider outreach of neuropsychology services to patients who are unable to travel to tertiary care centres due to financial constraints. This in turn could help provide continuity of care from a neuropsychological perspective in a country wherein neuropsychology is still in its nascent stages [10,62,63].

### Conclusion

Modifications in health care deliver can have profound implications on the validity of clinical trial data. To deal with the extenuating circumstance imposed by the COVID-19 pandemic and its impact on patients' ability to visit hospitals to complete data collection, we report mitigating strategies based on our situational and circumstantial context and limitations in India [16]. This paper sets the backdrop against which trial data, both qualitative and quantitative needs to be interpreted. To our knowledge, this is the first RCT on neuropsychological rehabilitation for patients with DRE in India.

### Ethical Statement

This material is the authors' own original work. A part of this work has been presented at 34<sup>th</sup> International Epilepsy Congress (virtual).

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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