Development of Digital Neuropsychological Battery: A Use Case in Indian SLE Patients

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CERTIFICATE

This is to certify that work presented in this thesis proposal titled ***Development of Digital Neuropsychological Battery: A Use Case in Indian SLE Patients*** by *Pragya Singhal* has been carried out under my supervision and is not submitted elsewhere for a degree.

Date

Advisor: Prof. Priyanka Srivastava

To family and friends

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Abstract

Despite India's history of 40 years of neuropsychology, cognitive and psychological testing is still in its infancy. The diverse needs of linguistically, culturally, educationally, and socio-economically varied populations have resulted in a significant underrepresentation within this domain. The existing assessments' gaps in applicability and reliability further compound the challenges faced in neuropsychological testing, especially in low and middle-income countries like India, characterized by diverse populations. To address the aforementioned challenges, we developed a prototype of a digital, language-independent neuropsychological test battery for a comprehensive assessment of cognitive health, psychological well-being, and quality of life. Our study specifically targets testing this battery among individuals affected by a complex autoimmune disease known as Systemic Lupus Erythematosus (SLE). SLE is a chronic disease that affects multiple organs in our body, including the central nervous system. This disease is frequently associated with a high prevalence of cognitive and psychological disorders, leading to a poor quality of life. Despite the increasing prevalence of SLE cases among the Asian population (range between 4.3-45.3/1 lakh), the neuropsychological data remain underrepresented. Factors such as poor consultant-to-patient ratio and inadequate tools to accommodate literacy, linguistic and cultural diversity hinder effective assessment.

This study investigated the psychological and cognitive health of Indian SLE patients using a customized test battery tailored to meet the needs of India's linguistically and culturally diverse population. A total of 102 SLE patients who met the 2012 SLE classification criteria volunteered to participate. The selection of SLE patient profiles was conducted by consultants who also provided the necessary medical records, including the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), to assess disease severity. Additionally, 105 healthy controls volunteered to participate, comprising two sub-groups: caregivers and college-going young adults. All the participants provided written informed consent, and the study was approved by Institutional Ethics committees. The battery comprised five cognitive tasks: Montreal Cognitive Assessment (MoCA) and indigenously oriented modified versions of the Attention Network Test (ANT), Sustained Attention to Response Task (SART), Picture Naming Task, and N-back working memory task. Additionally, it included five psychological tests: Patient Health Questionnaire (PHQ-9) for depression, Generalized Anxiety Disorder (GAD-7) for general anxiety, State-Trait Anxiety Inventory (STAI-T) for trait anxiety, Perceived Stress Scale (PSS-4) for stress, and World Health Organization Quality of Life (WHOQOL-BREF) for quality of life assessment. Results regarding psychological health indicated elevated levels of anxiety and stress among SLE patients,

coupled with a reduced quality of life across physical, psychological, social, and environmental domains compared to healthy controls. In terms of cognitive functioning, SLE patients exhibited impairments across multiple domains, including working memory, processing speed, executive functioning, sustained attention, and language proficiency, compared to healthy controls. Cluster analysis was used to identify factors that distinguished individuals within the SLE patient population to understand the heterogeneity associated with this complex disease. Our analysis revealed intricate correlations between mental health challenges in SLE patients and various factors such as social interactions, environmental influences, physical condition, age, education, and occupation. Furthermore, our analysis unveiled significant associations between disease severity (SLEDAI-2K), neuropsychiatric manifestations (NPSLE and non-NPSLE), education levels, and cognitive functioning in SLE patients. This comprehensive approach contributes to a deeper understanding of the complex interplay between psychological well-being, cognitive health, disease severity, demographic factors, and socio-environmental influences. It underscores the multifaceted nature of mental and cognitive health within the context of autoimmune disorders like SLE, paving the way for more targeted interventions and improved patient care strategies.

In summary, our study represents one of the pioneering efforts in comprehensively assessing the cognitive and psychological health of Indian SLE patients. Our work not only addresses the underrepresentation of Indian SLE patients in neuropsychological studies but also facilitates the advancements in neuropsychological testing in India, transcending language and cultural barriers. The development of a prototype for a digital, language-independent battery marks a significant step forward in neuropsychological testing within India, particularly where awareness and resources for such assessments are often lacking. Further, it is essential to focus on standardizing and validating this battery in young Indian adults to facilitate its widespread utilization.

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Chapter 1

Introduction

Have you ever experienced losing track of a conversation, forgetting where you kept something just a few moments ago, feeling anxious about your future or lacking motivation for daily tasks? These common lapses in attention, memory, anxiety and motivation are part of our everyday lives. While these lapses may seem harmless or attributed to boredom or absent-mindedness, they can also be indicative of more serious health issues, with potentially life-threatening consequences [1]. Notably, cognition is crucial in fundamental tasks such as eating on time, doing laundry, and grocery shopping. While a young, healthy adult might consider these tasks straightforward and manageable, these seemingly simple tasks can become daunting challenges due to various factors such as cognitive decline, memory impairments, and physical limitations resulting from a severe medical condition. This study focuses on one such disease known as Systemic Lupus Erythematosus (SLE).

Despite the frequently reported and observed cognitive decline by the consultants, cognitive testing remains at a nascent stage. The current landscape of cognitive and psychological testing faces significant challenges, such as the necessity of trained personnel for assessments and the absence of linguistically and culturally independent tests. Existing tests are predominantly designed from a Western perspective, lacking validation and standardization in linguistically and culturally diverse countries like India. Additionally, low and middle-income countries (LIMICs) often suffer from a shortage of trained professionals in clinical settings. To illustrate, consider the evolution of a thermometer, a device now accessible for laymen to measure their body temperature independently and accurately, without professional assistance. However, cognitive and psychological testing has not reached this level of accessibility and independence.

Hence, there is an urgent need to develop tests as simple as pressing a button, performing the test according to the instructions, and receiving results with interpretations. This study aims to address this need by developing a prototype for a digital language-independent battery that people from different cultures, ethnicities and countries can use to assess their cognitive and psychological health. Furthermore, this study focuses on testing this battery specifically within the context of Indian population, focusing on SLE patients, highlighting the necessity for tailored assessments in this demographic. The subsequent sections of this chapter will provide a general introduction to SLE, followed by an exploration of the neurological symptoms, including cognitive and psychological aspects associated with SLE.

1.1 Introduction to SLE

SLE stands out as a chronic autoimmune disease characterized by a diverse range of clinical manifestations, ranging from mild skin rashes to life-threatening organ involvement [2]. This heterogeneity underscores the dynamic nature of SLE, where each patient's experience is unique and warrants individualized management strategies. At its core, SLE is marked by unusual immunological responses, leading to the body's immune system turning against its own tissues. This dysregulation culminates in multi-system organ damage [3], necessitating continual monitoring to spot emerging or recurrent organ and systemic involvements. Moreover, it predominantly affects women and is associated with five times increased mortality compared to the normal population, with infections and cardiovascular events being the main causes of death [4].

SLE poses a significant diagnostic challenge owing to its diverse and frequently nonspecific symptoms. This complexity often results in delayed diagnosis and the potential for underdiagnosis [5, 6]. The aetiology of SLE remains uncertain, characterized by a complex interplay of genetic predisposition and environmental triggers [2]. The disease's pathogenesis involves the stimulation of B lymphocytes, the generation of autoantibodies, and the creation of immune complexes, which can lead to tissue damage [7, 8]. Additionally, CNS syndromes in SLE are often caused by ischaemia, antiphospholipid antibodies, and vasculitis [9]. In sum, SLE is a complex disease associated with various clinical presentations (including central nervous system involvement), aetiological factors and pathogenic mechanisms posing diagnostic challenges. The following section covers the diverse symptoms of SLE, focusing on the psychological and cognitive health issues associated with it.

1.2 Neurological Symptoms

SLE patients experience various symptoms, including severe fatigue, joint pain, swelling, headaches, rashes on the cheeks and nose (known as the "butterfly rash"), hair loss, anaemia, and blood clotting. The broad range of symptoms challenges diagnosis and understanding of the disease's aetiology. The distinctiveness of SLE resides not only in its clinical diversity but also in its ability to impact other organs in the body, including the central nervous system (CNS), adding complexity to diagnosis and treatment strategies. Research shows that CNS damage is a significant contributor to morbidity and mortality in SLE patients [10]. Remarkably, CNS involvement can occur early in the disease process, sometimes even before a definitive diagnosis of SLE is confirmed [11]. Studies show that 43% of children with SLE have CNS involvement, with certain patients experiencing late-onset manifestations, emphasizing the significance of monitoring neurological aspects in SLE management [12].

The American College of Rheumatology (ACR) nomenclature system acknowledges the manifestation of neuropsychiatric disorders in SLE disease. The neuropsychiatric syndromes of systemic lupus erythematosus (NPSLE) refer to the psychiatric impairment associated with SLE. NPSLE presents a spectrum of symptoms, spanning from non-specific manifestations such as headaches and cognitive impairment to severe outcomes like stroke and seizures [13, 14]. The pathogenesis of NPSLE is multifaceted, including autoantibody production, microvasculopathy, and pro-inflammatory cytokines [14]. The diverse array of symptoms and contributors to the disease's pathogenesis presents a formidable obstacle in the management of NPSLE. In sum, the complexity of associated dysfunctions contributes to the intricate nature of SLE, making it difficult for patients to comprehend the severity of their condition and seek timely medical consultation.

1.2.1 Psychological Health Issues Associated with SLE

The most commonly reported psychiatric disorders in SLE patients are acute confused state, anxiety, mood and psychosis, and emotion and mood regulation [15–17]. Multiple studies have focused on the psychological health issues associated with SLE and its high prevalence. In a recent study, 68% of SLE patients (n = 176) reported symptoms of depression, and 57.4% reported anxiety [18]. Notably, the reported psychological distress was observed in SLE patients even in the absence of apparent neuropsychiatric symptoms (non-NPSLE) [19]. When compared with rheumatoid arthritis (another autoimmune disease) and without autoimmune conditions, SLE patients reported higher distress than others [19]. In sum, the high prevalence of depression and anxiety in SLE disease, regardless of overt neuropsychiatric symptoms, emphasizes the heterogeneous nature of the NPSLE and impedes the timely diagnosis. Further, the prevalence of psychological symptoms among healthy young adults [20, 21] interferes with the diagnosis of SLE-related psychological health challenges.

Another factor that prevents the timely diagnosis of NPSLE or psychological health issues associated with SLE is stress. While the exact role of stress in the onset of SLE remains uncertain, its influence appears significant, intensifying the disease and notably impacting the quality of life for those affected [22]. Stress was found to predict fatigue, depression, and pain among this group, indicating its substantial role in contributing to multiple symptoms [23]. The presence of depression and anxiety and their strong association with stress in SLE patients underscores the urgency for holistic management approaches to address psychological disorders to improve the well-being of individuals navigating this complex autoimmune condition.

1.2.2 Cognitive Dysfunction Associated with SLE

SLE presents common and severe neuropsychiatric symptoms, spanning from subtle issues such as headaches and emotional disorders to more severe cognitive deficiencies. The spectrum of cognitive impairments associated with SLE includes a variety of domains essential for everyday functioning. Significantly, SLE patients struggle with deficits in set-shifting, conflict monitoring, visuospatial attention, sustained attention, working memory, language proficiency, autobiographical memory and abstraction [24–27]. The intersection between SLE and cognitive functions has gathered significant attention due to its widespread impact on affected individuals globally. Studies investigating cognitive dysfunction within the SLE patient cohort have demonstrated a vital evolution in prevalence rates. In a 1992 study, cognitive dysfunction was reported in 21% of SLE patients (n=80) [28], contrasting with a study in 2020, observing a significantly higher prevalence of 67.9% in patients (n=78) [29]. Furthermore, a 2023 study reported cognitive impairment in 70% of SLE patients (n=200) [30].

Our research focuses on the most commonly reported cognitive deficits associated with SLE, including executive functioning, processing speed, complex attention, language proficiency and working memory [31]. The choice of these deficits has been supported by neuroimaging studies, which have found associations between microstructural white matter abnormalities and these cognitive impairments [32]. Notably, SLE patients with neuropsychiatric manifestations (NPSLE) exhibit poorer performance on tasks assessing complex attention, consistent with findings from neuroimaging studies linking these deficits to white matter abnormalities [31]. Moreover, investigations have revealed a correlation between impaired working memory and left frontal lobe white-matter atrophy in SLE patients [33]. Additionally, slower processing speed, observed in both NPSLE and non-NPSLE individuals, has been strongly correlated with white matter integrity [34]. In light of the reviewed literature, our test battery has been meticulously designed to address the frequently reported cognitive impairments associated with SLE.

The complexity of SLE lies in its heterogeneous presentation and the uncertain course it takes, making it a challenging disorder to diagnose and manage [35]. The symptoms experienced by individuals with SLE are characterized by their diversity and varying frequencies. This heterogeneity is especially prominent in neuropsychiatric systemic lupus erythematosus (NPSLE), with a reported prevalence ranging between 6% to 91% [36]. Research consistently highlights the significant diversity in NPSLE symptoms, encompassing a broad spectrum of clinical phenotypes and frequencies [37, 38]. In addition to the diversity observed in symptoms, SLE exhibits a remarkable heterogeneity in terms of affected demographics. The subsequent section focuses on the increasing global prevalence of this disease and the affected demographics, emphasizing the critical and urgent need for neuropsychological testing of SLE patients. We also highlight the current situation of SLE in India, shedding light on the underrepresentation of the Indian SLE population.

1.3 Global and Indian Prevalence

The rising incidence of SLE worldwide [36] and within the Indian population highlights an escalating concern regarding its impact on the cognitive and psychological health of patients. The prevalence and incidence ratios for SLE range from 3.2 to 3000 per 100,000 and 0.3 to 8.7 per 100,000 persons, respectively [39, 40]. A more recent study reports that the prevalence of SLE is estimated to be 43.7 per 100,000 persons, affecting approximately 3.41 million people [41]. Notably, the highest prevalence rate is associated with the age range between 20–49 years, with a wide geographical variation in SLE's reported incidence and prevalence [42]. Studies have shown the variation in prevalence rates across different countries, with the highest rates reported in North America and the lowest in regions like Africa and Ukraine [42].

Moreover, the disparity in SLE prevalence extends beyond mere numbers, with a striking gender imbalance observed [43]. Women are disproportionately affected by SLE, with reports indicating a staggering women-to-men ratio of 7-15:1 for adults and 3–5:1 for pediatric patients [44]. A recently published report [45] presents similar statistics from Taiwan, covering the nationwide population using a longitudinal paradigm. They reported 14.3 per 10,000 females and 1.62 per 10,000 males diagnosed with SLE between 2001-2011 [45]. This gender disparity is striking, with a higher prevalence among women of reproductive age, necessitating tailored, sex-specific care approaches [46]. Estrogen might be implicated in the aetiology of SLE, yet the precise mechanisms underlying their role in modulating the immune system remain elusive, warranting further investigation [47]. Furthermore, studies underscore the pronounced heterogeneity of SLE across various ethnic groups [43]. For instance, research conducted in the UK revealed significantly higher prevalence rates among Afro-Caribbean females (206.0/100,000) compared to the general population (27.7/100,000), irrespective of place of birth [48]. Similarly, another study shed light on the early onset of SLE in East-Asian ethnic groups and the persistently high prevalence among Afro-Caribbean patients [49]. Studies in New Zealand [50] and the United States [51] have found higher prevalence rates in Polynesian and black populations, respectively, compared to white populations.

In the Indian context, the reported prevalence rate of SLE stands at 3.2 per 100,000 individuals [39]. Notably, India ranks among the top countries with the largest female and male populations with newly diagnosed SLE, trailing only behind China [41]. Considering the escalating prevalence and incidences of SLE, there is a significant dearth of comprehensive cognitive and psychological data, specifically for the Asian and Indian populations. Given that SLE affects young adults in their productive years, it adds to the national burden of diseases in young individuals, who are crucial contributors to the country's development and prosperity, underscoring the critical nature of this problem.

1.3.1 Underrepresentation of Indian Population

Despite the high prevalence, there exists a notable deficiency in standardized assessment tools specifically designed to effectively screen and potentially treat cognitive impairments within the Indian SLE patient demographic. The existing standardized assessments lack representation from diverse ethnic, linguistic, and regional groups within India. This under-representation can lead to a lack of normative data for specific subpopulations, reducing the assessments' accuracy for those groups. It has been found that the complexity of the educational system, linguistic diversity, and infrastructural deficiencies impede the development of indigenous intelligence tests for the Indian population [52]. The 2001 consensus reported 122 major languages and 1599 other languages in India, of which 30 languages were spoken by more than a million native speakers [53]. Furthermore, India has the world's largest illiterate population (287 million), with 37% of the world total [54].

This skewed representation, coupled with the contrasting prevalence reporting of SLE cases in low and middle-income countries (LIMICs) like India, poses a serious threat to NPSLE diagnostics. Furthermore, the lack of linguistically agnostic neuropsychiatric screening tools, digitized health support, scarcity of neuropsychiatric professionals [55], societal stigma surrounding psychological health, socioeconomic constraints, and cultural recognition of such issues collectively compound the challenge [56] and hinder effective monitoring and support for Indian SLE patients. This notable absence raises critical concerns and emphasizes the urgent need for targeted research efforts to address the cognitive and psychological facets of SLE among the Indian population.

1.4 Challenges in Cognitive and Psychological Assessment of Indian SLE Patients

1.4.1 Existing English-centric Assessment Tools

The existing standardised neuropsychological tests, such as the Montreal Cognitive Assessment (MoCA), Wechsler Adult Intelligence (WAIS-R) and Stroop Colour and Word Test are effectively useful tools for cognitive assessment on a global scale [57–59]. However, their dependence on the English language poses serious challenges when used in linguistically and culturally diverse settings like India. Studies have underscored the influence of culture, language, and education on the validity and utility of these tests and the necessity for culturally adjusted assessments with education-specific 'cut-offs' for informed clinical decision-making [60]. Notably, research shows the need for population-based norms and cut-offs for MoCA [61]. Similarly, potential preferences for cultural variables have been highlighted in a study comparing Kuwaiti and British subjects, with Kuwaiti students displaying greater interference in the Stroop Color and Word Test [62].

One reason for these biased results could be the presumption of some level of language proficiency in these English-centric assessments, possibly disadvantaging individuals who are fluent in regional languages other than English. The use of western culturally specific references and idioms in these assessments may lead to misconceptions or a lack of familiarity among people from different cultures. Hence, assessments developed from a Western perspective may fail to account for cultural diversity, producing biased outcomes. In the specific context of assessing cognitive impairments in Systemic Lupus Erythematosus (SLE) patients, the American College of Rheumatology (ACR) introduced a standardized neuropsychological battery [63]. However, this battery is designed primarily for English-speaking populations, making it unsuitable for culturally, ethnically, and linguistically diverse groups. Consequently, there is a growing focus on research efforts aimed at developing new tests that can effectively evaluate cognitive impairments in underrepresented populations [64].

1.4.2 Paper-Pencil Tests Administration

The dependence on traditional paper-pencil-based neuropsychological assessments adds another layer to the challenges faced in the context of cognitive evaluations, particularly in the diverse and dynamic setting of India. Paper-pencil tests often require skilled clinicians or professionals for administration, increasing the dependence on healthcare professionals. This reliance can limit the scalability of assessments, especially in regions with a shortage of trained personnel. For example, low and middle-income countries (LIMICs) like India have only 0.75 Psychiatrists per 100,000 population in contrast to the figures of 6 Psychiatrists per 100,000 population in high-income countries [55]. Additionally, these assessments may be perceived as monotonous and lacking patient engagement, potentially affecting the accuracy of the results. Moreover, paper-pencil tests offer limited opportunities for real-time monitoring of cognitive functions. The manual nature of paper-pencil tests restricts their application outside clinical settings, limiting the scope for continuous evaluation and follow-up care.

Computerized cognitive assessments offer significant advantages over traditional testing methods, particularly regarding user experience and usability [65, 66]. These assessments facilitate the accurate recording of user responses, including response times, and provide automated, unbiased feedback and instant results. Moreover, they support the integration of more sophisticated techniques, such as eye movement detection and functional imaging, enhancing the depth and precision of cognitive evaluations [66]. Comprehensive digitization of health records is pivotal for efficient data management and accessibility, ultimately improving the overall quality of patient care. Digital solutions in cognitive assessment not only streamline the process but also enhance accessibility, reaching a broader population. This indicates that digital solutions are the future of cognitive testing, offering improved efficiency and accessibility to diverse demographics. Furthermore, digitization enables us to integrate advanced techniques such as machine learning algorithms for prediction and deep learning for assessing brain imaging, among others. This creates a promising foundation for future advancements in cognitive assessment [67].

1.5 Objective

The primary objective of this study is to develop a prototype of a comprehensive neuropsychological test battery to assess cognitive and psychological health in the use case of patients with Systemic Lupus Erythematosus (SLE). This research represents a pioneering effort within the Indian context, addressing the longstanding issue of underrepresentation of the Indian SLE population in neuropsychiatric studies. By addressing factors such as literacy, language, cultural nuances and technological adoption, the broader aim is to develop assessments that are not only scientifically robust but also relevant and accessible to a broad spectrum of individuals. Our study aims to bridge the gap between existing assessments and the distinct needs of the Indian population, ensuring language-agnostic digital neuropsychological test battery for cognitive and psychological assessment.

1.6 Thesis Organisation

This thesis is divided into five chapters, which are organized as follows:

- **Chapter 1 (This Chapter)** sets the stage by providing background information on systemic lupus erythematosus (SLE) and discussing the inherent heterogeneity associated with this condition. It outlines the research gaps existing in the field of cognitive and psychological assessment of SLE patients in India and elaborates the overarching objectives of our thesis.
- **Chapter 2** provides a detailed account of the development process behind our neuropsychological battery. We navigate through the challenges encountered during the initial design phase and explain the strategies implemented to overcome them. Additionally, we explore two pivotal sub-studies conducted alongside the main study, which played integral roles in shaping our final battery design.
- **Chapter 3** focuses on the comprehensive psychological assessment of SLE patients. We outline the methodology for the assessment, present the findings from the study, and draw insightful inferences based on the outcomes.
- **Chapter 4** focuses on the cognitive assessment of SLE patients. Similar to Chapter 3, we delve into the methodological aspects of the assessment process, present the results obtained, and elaborate on the implications derived from the analysis.
- **Chapter 5** concludes the thesis by summarizing our work and outlining potential future research in the field of neuropsychological assessments.

Chapter 2

Development of Digital Neuropsychological Battery

Despite India's history of 40 years of neuropsychology [68], cognitive testing is still in its infancy. The complexity of the educational system, linguistic diversity, and infrastructural deficiencies have hindered the development of indigenous intelligence tests [52]. With 122 major languages and 1599 other languages in India, of which 30 languages were spoken by more than a million native speakers [53], alongside a staggering illiterate population of 287 million [54], India's diverse population faces unique challenges in cognitive assessment.

Hence, we aim to develop a language-independent neuropsychological battery to fit the diverse needs of the Indian population. The current chapter delves into the developmental trajectory of our digital neuropsychological test battery, tailored to evaluate prevalent cognitive and psychological health issues among SLE patients. The development process was divided into several phases. Below is a brief overview of these phases to showcase the thoughtful approach taken in designing this battery.

2.1 Phases of Development

- **Phase 1:** The first phase focused on performing a thorough literature review of studies related to cognitive and psychological impairments associated with SLE. This enabled us to pinpoint the prevalent cognitive and psychological issues reported in SLE patients, as discussed in the first chapter, along with the assessment tools typically utilized. We extensively reviewed existing tests and batteries to identify commonly employed assessments and the targeted population. A detailed description of these tests is provided in the section 2.2 (Literature Review).

- **Phase 2:** After identifying common cognitive and psychological issues in SLE patients, as well as potential challenges in existing tests, we focused on developing tests customised to our specific population. We aimed to create tests that were comfortable for users and spent ample time translating them into native languages like Telugu and Hindi to accommodate our linguistically diverse population. We conducted small pilot tests with college students to test these translated versions. Additionally, significant effort was devoted to writing clear instructions for the tests to ensure understanding among our participants. In addition to traditional instructions, we used paper cards and coloured stickers on laptop keys (e.g., a red sticker on the 'R' key) for participants' reference. The details of our initial battery design are discussed in section 2.3, followed by a Pilot Study at the NIMS Hospital in section 2.4.

- **Phase 3:** Following the pilot study, we worked on resolving the challenges encountered during the initial battery design phase. This involved developing a new battery by adding, removing, and modifying certain tests. The comprehensive overview of our new battery design, including details about the tests that were changed and the rationale behind these modifications, is also discussed in this chapter. Additionally, we conducted two sub-studies to validate and enhance the effectiveness of the new design. These efforts were aimed at refining our approach and ensuring the reliability and accuracy of the cognitive assessments in our battery.

- **Phase 4:** The final phase involved conducting field visits to collect data, followed by a thorough analysis. This phase signifies the completion of our project, which aimed to develop a prototype for a neuropsychological test battery tailored to meet the diverse needs of our target users.

2.2 Phase 1: Literature Review

We did an extensive literature review to examine the studies focusing on the psychological and cognitive deficits in sle patients. We delved into studies focusing on neuropsychological testing, neuropsychiatric symptoms, depression, anxiety, quality of life, working memory deficits, attentional deficits, cognitive dysfunction and meta-analysis, among other relevant keywords. This comprehensive search was conducted across platforms like Google Scholar, PubMed, and Elicit. Our findings revealed a common trend among the studies, with a predominant focus on a patient demographic aged between 20 to 55 years. These studies often featured sample sizes ranging from 20 to 200 individuals, with more than 90% of the patients being females [18, 19, 24, 69]. Notably, the literature revealed a geographical bias, with the majority of studies originating from regions outside of Asia [19, 69]. Meta-reviews supported this observation, pointing to a gap in research within the Asian context, particularly regarding SLE-related psychological and cognitive impairments [70]. However, we also found valuable insights from a few studies conducted in China and Japan, contributing to a more global understanding of these issues. [18, 24]. Through these sources, we aimed to contextualize our research within the broader landscape of SLE-related psychological and cognitive studies, emphasizing the need for more region-specific investigations.

Our comprehensive literature review allowed us to identify the commonly reported cognitive and psychological dysfunction in SLE patients. SLE has been associated with a spectrum of psychological disorders such as acute confused state, depression, anxiety, mood and psychosis, and emotion and mood regulation [15–18]. Hence, widely accepted self-reported surveys were employed to assess the psychological well-being of SLE patients, as detailed in Chapter 3. Additionally, common cognitive deficits observed in SLE patients include executive functioning, processing speed, complex attention, language proficiency and working memory [31]. While numerous tests exist for evaluating these cognitive deficits, most of them are non-digitized, requiring trained personnel for administration, and pose challenges related to language fluency, cultural relevance, and literacy levels. Table 2.1 outlines some of the commonly used tests and test batteries for assessing cognitive dysfunction in SLE patients, highlighting the aforementioned limitations.

Table 2.1 Existing Neuropsychological tests

Tests	Cognitive Functions	Digital	Linguistically and Culturally Independent
Trail Making Test (TMT)	visuomotor skills, executive function, processing speed, cognitive flexibility,	NO	NO [71]
Wechsler Adult Intelligence Scale (WAIS-R)	comprehensive test to measure general cognitive and intellectual functioning	NO	NO [72]
Victoria Stroop Test	attention, executive function	YES	NO [73]
Benton Visual Retention Test (BVRT)	visual perception and visual memory	NO	NO [74]
Hopkins Verbal Learning Test	verbal learning and memory	NO	NO [75]
N-back Working Memory Task	working memory	YES	NO [76]
California Verbal Learning Test (CVLT)	repetition learning, serial position effects, semantic clustering	NO	NO [77]
Finger Tapping Test	psychomotor speed	NO	YES
Montreal Cognitive Assessment (MoCA)	assessment for screening of mild cognitive impairment	NO	NO [61]
ACR-NB	battery of 10 tests to measure various cognitive functions	NO	NO [16]
ANAM	battery of 22 tests to measure various cognitive function	YES	NO

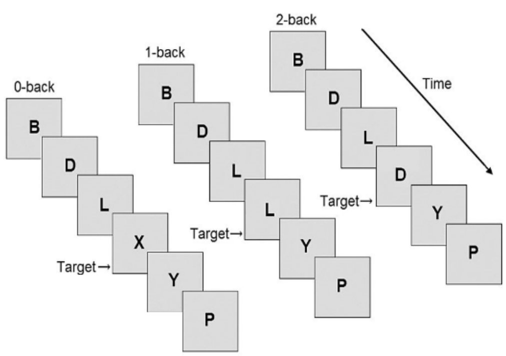
One of the prominent test batteries is the American College of Rheumatology Neuropsychological Battery (ACR-NB), designed specifically for assessing cognitive impairment in SLE patients. It comprises ten cognitive tasks targeting various cognitive domains such as motor speed, attention, executive function, cognitive flexibility, memory, etc. [78]. Tests used in ACR-NB include the Wechsler Adult

Intelligence Scale (WAIS-R and WAIS-III), Trail-making Test (TMT-A and TMT-B), California Verbal Learning Test (CVLT), Rey-Osterrieth Complex Figure Test (RCFT), Finger Tapping Test, Stroop Color and Word Test, Controlled Oral Word Association Test (COWAT) and Animal Naming Test [79]. Another notable test battery is the Automated Neuropsychological Assessment Metrics (ANAM), with 22 tests covering a range of cognitive domains, including attention, working memory, continuous performance, cognitive flexibility, spatial processing, etc. [78]. Though ACR-NB is a widely used test battery, it is an hour-long battery that is paper-pencil-based and requires trained personnel for administration. Moreover, it has been standardised only for English-speaking patients [16]. Its dependence on language and administrative burden makes it less feasible in countries like India. While ANAM addresses some administrative challenges by digitizing the tests, its language-dependent nature lacks validation and standardization in India, limiting its applicability in our context [78].

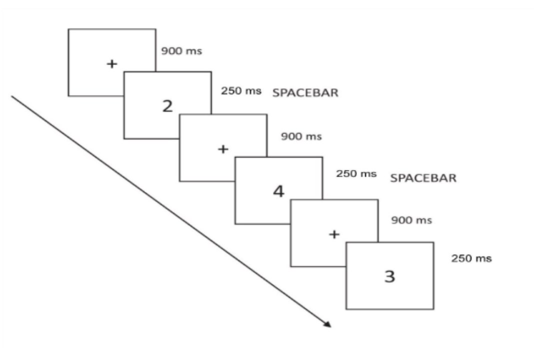
Despite the diverse needs of the Indian population, there have been relatively few initiatives in India aimed at developing contextual neuropsychological test batteries. The National Institute of Mental Health and Neurosciences (NIMHANS) initiated the development of a neuropsychology battery specifically for India [80]. However, these tests lack standardization and validation, posing challenges to their widespread use and reliability. Additionally, the Indian Council of Medical Research (ICMR) developed the ICMR-Neurocognitive Toolbox (ICMR-NCTB) protocol, introducing cognitive and functional tests in five Indian languages and designed to accommodate varying literacy levels across the country. While this initiative is commendable, this battery is not completely language-independent, and its effectiveness in diagnosing conditions like dementia within the illiterate population remains to be established [81]. Another drawback of the ICMR-NCTB is its limitation to function solely as a screening tool, akin to the Montreal Cognitive Assessment (MoCA) [57], without providing detailed insights into the severity of cognitive dysfunctions. Furthermore, there is limited evidence supporting the applicability of these test batteries in the specific context of SLE patients. Given the gaps and limitations in existing neuropsychological test batteries in India, our research endeavours to fill this void by developing a comprehensive language-independent digital test battery. We aim to adapt previously utilized cognitive tests for SLE patients, making necessary modifications to suit the Indian population's linguistic and cultural diversity.

2.3 Phase 2: Initial Battery Design

The choice of assessments in the initial battery design was done after a thorough review (Table 2.1) of the literature to include the commonly reported psychological and cognitive deficits in SLE patients. This was done in consultation with the senior medical professional, Dr. Liza Rajasekhar, Head of the Department of Clinical Immunology and Rheumatology. The initial battery design comprised the following questionnaires for the psychological assessment: the Patient Health Questionnaire (PHQ-9) for depression, the Generalized Anxiety Disorder Assessment (GAD-7) for general anxiety, the Perceived Stress Scale (PSS-4) for stress, the Spielberger State-Trait Anxiety Inventory (STAI-T) for trait anxiety, and the World Health Organization Quality of Life Brief Assessment (WHOQOL-BREF). In addition to this, participants were asked basic questions about orientation, including the day, date, time, and place of assessment. Cognitive assessments comprised four key tasks: N-back task for working memory, Sustained Attention to Response task (SART) for sustained attention, Stroop Color test for executive functioning (conflict monitoring) and Wisconsin Card Sorting for set-shifting. A colour-blindness assessment was also conducted to ensure participants' suitability for tasks such as the Stroop and Wisconsin Card Sorting tasks, which necessitate the ability to recognize differences among colours. To ensure the inclusivity and relevance of our assessments to our population group, we designed the N-back and Stroop tests in three languages: English, Hindi, and Telugu. However, the SART task was used in its traditional form, which utilized English digits as stimuli. Furthermore, the Wisconsin Card Sorting task, which traditionally uses shapes as stimuli, remained unchanged in this aspect.

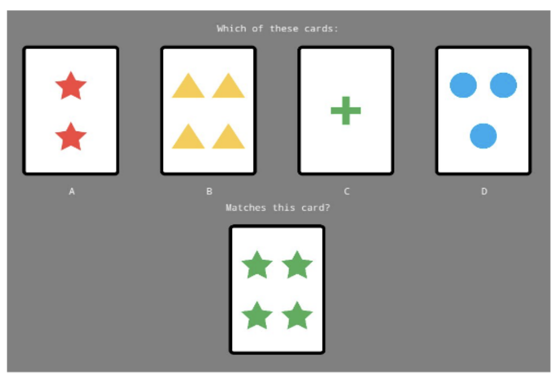


(a) N-back Task



(b) Sustained Attention to Response Task (SART)

(c) Stroop Task



(d) Wisconsin Card Sorting Task

Figure 2.1 Initial Battery Design

2.3.1 N-Back Working Memory Task

N-back is a widely used task for measuring working memory. In this task, participants are presented with a sequence of stimuli (alphabets in their preferred language) one at a time on a computer screen (Figure 2.1). The participant's task is to indicate whether the current stimulus matches the one presented

”n” steps back in the sequence, where ”n” can be 0,1 or 2. In the 0-back condition, a stimulus is considered the target if it matches a specific target stimulus presented at the beginning of the task (0th trial). For the 1-back condition, a stimulus is considered a target if it matches the one immediately preceding it (1 trial back). Similarly, for the 2-back condition, a stimulus is considered the target if it matches the one presented two steps earlier in the sequence (2 trials back). The traditional N-back task typically utilizes English alphabets as stimuli; however, we modified this to incorporate Hindi and Telugu alphabets in their respective versions.

2.3.2 Stroop Color Task

Stroop is widely used for assessing executive functions, such as conflict monitoring. In this task, participants are presented with words printed in coloured ink, such as red, green, blue, and yellow, and are asked to name the ink colour while ignoring the word itself (Figure 2.1). There are three main conditions: the congruent condition, where the word displayed on the screen matches the ink colour it’s printed in (for example, the word ”Blue” displayed in blue ink); the incongruent condition, where the word displayed is different from the colour of the ink (for example, the word ”Red” displayed in blue colour); the neutral condition where the word displayed is not colour-related (for example, the word ”Dog” displayed in blue colour). The Stroop effect refers to the phenomenon where participants typically exhibit longer response times and higher error rates in the incongruent condition compared to the congruent and neutral conditions. Similar to the N-back task, the Stroop Color task, which typically employs English words, underwent modification to feature Hindi and Telugu words for their respective versions.

2.3.3 Sustained Attention to Response Task (SART)

SART measures the participant’s ability to maintain sustained attention over an extended period while continuously monitoring and responding to the stimuli (inhibition and vigilance). In this task, participants are presented with a sequence of stimuli, typically digits (e.g., 1 through 9), presented one at a time on a computer screen (Figure 2.1). The participant’s task is to respond to each digit by pressing the ”SPACEBAR” key, except when a specific target digit appears. In the standard version of the task, the target digit is often ’3’. Participants are instructed to withhold their response when encountering the target digit and only respond to all other digits.

2.3.4 Wisconsin Card Sorting Task (WCST)

WCST is a widely used task for measuring cognitive flexibility and set-shifting. In this task, participants are presented with a set of cards that vary in colour, shape, and number. They are then instructed to match these cards according to specific sorting principles like colour, shape, or number. However, the sorting principles are not explicitly disclosed to the participants. Instead, they must infer the correct sorting principle based on feedback provided after each sorting attempt. As the task progresses, the sorting principles are periodically changed without warning, requiring participants to adapt their strategies accordingly. The ability to flexibly shift between different sorting principles and to learn from feedback is essential in this task, hence measuring the participant's cognitive flexibility and set-shifting abilities. The traditional version of WCST is a paper-pencil task where the participants are presented with a deck of cards, and the administrator provides feedback based on the participant's response. We created a digital version of this task (Figure 2.1), aligning with our future objectives such as integrating technologies like eye-tracking.

2.4 Pilot Study

The development of the selected tests into their digital versions was followed by a pilot study conducted at NIMS Hospital. This marked our initial venture into the field with a fully developed battery. Before this, we had to interact with patients on our field visits to understand the expected patient profile and to discuss the battery design and data collection procedure. Detailed methodology, along with a summary of the results and their insights, are presented in the subsequent sub-sections.

2.4.1 Method

A pilot study was conducted at the NIMS Hospital with seven SLE patients (*Median Age = 21, F = 100%*). Three participants had received less than ten years of formal education and spoke only Telugu, while the remaining participants had more than ten years of education and could speak/understand Hindi or English in addition to Telugu. Before commencing the study, all participants received detailed information regarding the study objectives, procedures, voluntary participation, and the confidentiality of their data. Participants were also informed about the voluntary nature of participation, including the right to withdraw from the study at any point without facing consequences regarding medical support from the hospital. Informed consent was obtained from each participant, affirming their willingness to participate in the study. Each participant was assigned the cognitive and psychological assessments in a random order. Additionally, participants were asked their preferred language for assessment, which was used for all the cognitive tasks and instructions. In addition to completing the cognitive and psychological tasks, participants' demographic information and relevant medical information pertaining to the participants' SLE diagnosis and treatment history were documented.

2.4.2 Summary of Results

The N-back task revealed an expected trend in accuracy as the difficulty level increased. Participants exhibited a decreasing trend in accuracy from an average of 92.6% in the 0-back condition to 90.3% in the 1-back condition and 80.7% in the 2-back condition. This observed decrease suggests a memory-related load effect, wherein cognitive performance declines with increased cognitive demand.

Moreover, participants exhibited a corresponding increase in reaction time as the difficulty level of the N-back task escalated from 0-back condition (*M* = 1.946 *seconds*) to 2-back condition (*M* = 2.029 *seconds*), aligning with the previous literature [82]. In the Stroop task, participants demonstrated varied performance, showing a range of Stroop effects (incongruent reaction time - congruent reaction time) from -29.6 *milliseconds* to 143.6 *milliseconds*. These results did not provide clear conclusions regarding impairments in executive functioning among the participants. Participants' performance in the SART task was characterized by poor total accuracy (*M* = 89.4%), accompanied by high commission (*M* = 45.1%) and omission errors (*M* = 6.2%). Additionally, results from the Wisconsin Card Sorting Task revealed a mean accuracy of less than 60% (*M* = 55.8%). Interestingly, despite the low overall accuracy, the observed average perseveration error (errors resulting from repeatedly applying the same rule) was only 0.06%.

Despite the limited sample size, we observed diversity in the languages chosen for test administration, with 43% of participants (n = 3) opting for Telugu, 43% (n = 3) for English, and 14% (n = 1) for Hindi. This diversity is expected to increase with a larger sample size due to India's rich linguistic diversity. However, the varied languages in which participants attempted the tests and the lack of standardized tests across multiple languages limit the strength of inferences that can be drawn from these results. Therefore, cognitive testing in India's multilingual population necessitates test standardization across various languages.

2.4.3 Conclusion

The pilot study provided valuable insights into the challenges faced during cognitive testing among our patient population. One of the major setbacks was the language dependence of the Stroop task. Although we translated the task into Hindi and Telugu alongside English, we encountered the limitation of lacking normative data for comparison. This absence of baseline data across multiple languages limits the reliability and validity of the Stroop task, particularly in India's linguistically diverse context. Standardizing the Stroop task across various languages would be necessary for its widespread use in India, a task beyond the scope of our project. Moreover, as the Stroop task heavily relies on the conflict arising from incongruent word-colour associations, participants with limited reading abilities may not experience the typical interference effect expected in the incongruent condition. Therefore, the usability of the Stroop task within India's linguistically and educationally diverse population is constrained.

Additionally, our participant population exhibited lower performance levels in the N-back task compared to the data from previous studies involving SLE patients. This observation led to a critical inquiry into potential contributing factors, including the diverse languages used during the test administration. For instance, a US-based study from 2007 utilized the N-back task to assess the working memory of SLE patients in New York [82]. While the trends in accuracy were similar to our results, the reaction times in this study were significantly lower, with a mean reaction time of 0.96 *seconds* in the 2-back condition, contrasting sharply with the 2.029 *seconds* exhibited by our population. These findings, once again underscore the importance of standardizing tests across different languages and having normative data for comparison.

The Stroop and N-back results highlighted that translating tests into different languages would not suffice due to the lack of standardization across languages. This poses a complex challenge because direct comparisons between data collected in different languages could obscure the true source of differences observed in results. In other words, it would be challenging to distinguish between cognitive impairments and language-related variations. Thus, the scarcity of standardized tests limits our ability to accommodate various languages in a single test, as each language script may require different processing times. To delve deeper into this issue, a small pilot study was conducted with three college students proficient in English and Hindi. Participants attempted the Stroop, N-back and SART tasks in both languages. The results of this study provided compelling evidence of the impact of language on test outcomes (Table 2.2). Significant differences in accuracy and reaction times were evident between the English and Hindi versions of the same tasks, emphasizing the impact of language-related differences on performance, as supported by previous literature [83].

Table 2.2 Average cognitive Scores (Mean) from the pilot study (n = 3) in English and Hindi languages.

Cognitive task	English	Hindi
Stroop Accuracy (%)	91.25	93.33
Stroop Reaction Time (ms)	902.01	1110.88
0-back Accuracy (%)	80.5	73.3
0-back Reaction Time (ms)	612.75	561.3
1-back Accuracy (%)	78.5	79.3
1-back Reaction Time (ms)	683.54	634.43
2-back Accuracy (%)	76.5	70.0
2-back Reaction Time (ms)	651.88	739.61
SART Accuracy (%)	95.47	90.68
SART Commission Errors (%)	25.0	55.82
SART Omission Errors (%)	1.96	3.82
SART Reaction Time (ms)	323.76	240.48

In sum, these findings suggest that the current tasks, in their traditional form, may not be suitable for populations with diverse characteristics. Translating the assessments into local languages is not an ideal solution as it requires standardization due to the absence of normative data across multiple languages. Moreover, translating the assessments into local languages does not effectively address the challenges faced by individuals with low levels of education. Consequently, our pilot study highlights the importance of considering participants' linguistic, cultural, and educational backgrounds when selecting cognitive assessment tools. While these tasks remain valuable in many contexts, their effectiveness may vary depending on the target population's literacy levels and cultural nuances. Hence, there is a need for the development of language-independent cognitive tests capable of reaching a broader audience and achieving global standardization. By transcending linguistic barriers, such tests can mitigate the impact of education, language, and culture on cognitive assessment, thereby yielding clearer insights into the cognitive effects of SLE.

2.5 New Battery Design

The design of our final battery was marked by meticulous considerations and strategic priorities. Firstly, our battery design was guided by a thorough review of existing literature and prevalent cognitive and psychological disorders observed in SLE patients. Aligning with this research, our battery prioritized the integration of assessments for the most relevant and frequently reported cognitive dysfunctions and psychological disorders observed within the SLE patient population. The psychological assessments included initially were used as they are (Figure 2.3). Secondly, our battery design meticulously considered the total assessment time to mitigate participant fatigue and uphold data quality. Lastly, the results of our pilot study prompted significant changes in addressing the needs and challenges encountered by our linguistically, educationally and culturally diverse participant population.

Consequently, the decision was made to remove the Stroop task from the battery, recognizing their limited suitability for individuals with varying education and language proficiency levels. Additionally, the Wisconsin Card Sorting task was removed to limit the time of assessment. As a result, the colour-blindness assessment, initially intended for these tasks, was also discontinued. Our renewed battery design emphasized the importance of assessing language proficiency alongside key cognitive functions such as working memory, executive functioning, and attention. To achieve this, we integrated the Picture Naming task into our battery, extensively evaluating participants' linguistic abilities. Furthermore, we introduced a revised version of the N-back and SART tasks, utilizing daily life objects as stimuli instead of the traditional English alphanumeric characters. This strategic adaptation aimed to provide more contextually relevant and inclusive stimuli not only for our population but also for a broader global audience. Additionally, we incorporated the Attention Network Task (ANT) into our battery instead of the Stroop task to assess executive functioning along with alertness and orientation. Recognizing the importance of culturally sensitive stimuli, we updated the traditional ANT (using arrows as stimuli) to utilize trucks as stimuli, aligning with our commitment to contextual relevance and inclusivity. Along with the detailed cognitive assessments targeting specific cognitive functions, we included the Montreal Cognitive Assessment (MoCA) in both English and Hindi. The idea was to utilize MoCA as a benchmark tool for validating the outcomes derived from other detailed cognitive assessments. Each task is meticulously detailed in Chapter 4, offering a comprehensive overview of their methodologies and objectives.

The new battery design was formulated under specific constraints, such as recruiting participants with at least a secondary level of education (10th class) and avoiding purely Telugu-speaking participants for the main study. This cautious approach stems from the absence of a benchmark to compare cognitive and psychological data across linguistically diverse populations. Given that this study serves as the initial phase in designing and testing the prototype, these constraints were necessary to ensure a standardized and comparable dataset.

In selecting daily-life objects for the N-back and SART stimuli, we conducted a familiarity study to identify highly familiar objects rated by participants. This process ensured that the stimuli used in our assessments were culturally relevant and easily identifiable across diverse populations. Moreover, we conducted a thorough validation study to validate the new versions of the N-back and SART tasks, affirming their reliability in measuring cognitive function across our participant cohort. In the subsequent sections, we will delve into the details of these two sub-studies, shedding light on the methodologies employed and the insights gained, thereby providing a comprehensive understanding of the evolution of our cognitive battery design.

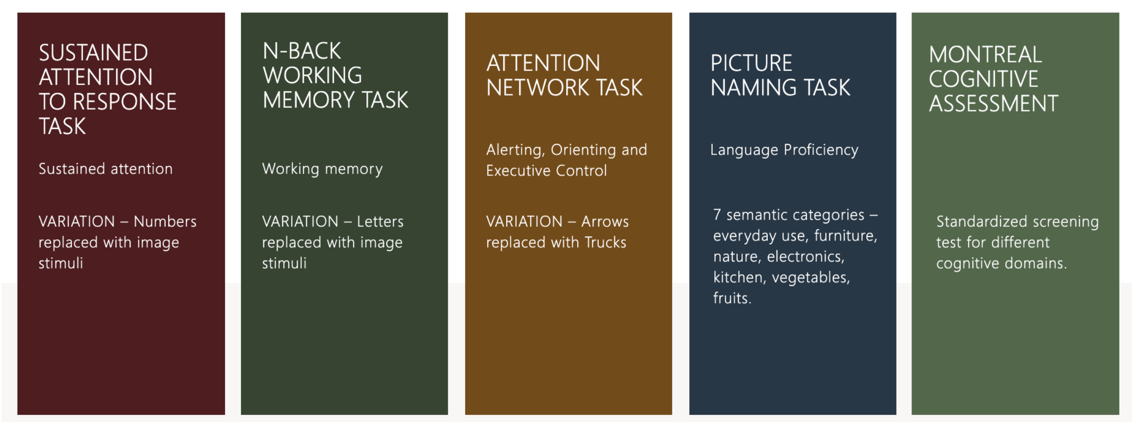


Figure 2.2 Cognitive Assessments of the Final Battery Design

Figure 2.3 Psychological Assessments of the Final Battery Design

2.6 Familiarity Study

2.6.1 Introduction

The selection of appropriate stimuli is critical when developing a new version of the N-back and SART task with the objective of eliminating language barriers. The rationale for this study stems from the observation that traditional stimuli such as English letters may pose challenges for individuals with limited language proficiency, hindering the validity and reliability of cognitive assessments. To address this issue, we embarked on a familiarity study to identify the widely recognized and contextually relevant everyday objects for inclusion in our cognitive tasks. The primary objective of this study is to identify objects that transcend cultural, linguistic, and educational barriers, ensuring accessibility and relevance across diverse populations.

2.6.2 Methods

A total of 52 volunteers participated, representing diverse demographics to ensure inclusivity and relevance across populations. The participants were divided into three groups to capture a spectrum of language proficiency, education levels, and socioeconomic backgrounds. The first group consisted of twenty-two individuals who were the caregivers (family members) of the patients visiting NIMS Hospital, who had a demographically matched profile with the SLE patients, representing the rural population of India. The second group comprised fifteen housekeeping staff members from IIIT Hyderabad, representing the lower-middle-class urban population. This group offered diversity in terms of education, language, and socioeconomic status. The third group comprised fifteen bachelor's degree students from IIIT Hyderabad, representing the upper-middle-class urban population. Well-versed in English with higher education levels and economic profiles, this group provided insights into the familiarity of objects among a more privileged demographic.

To assess familiarity, participants were presented with a collection of thirty-two objects categorized into five semantic categories: general everyday use objects, nature, kitchen, electronics and furniture (Table 2.3) to ensure inclusivity and contextually relevant objects. They were asked to rate the familiarity of the object on a 3-point Likert scale, with one being the least familiar and three being the most familiar. This methodology ensured comprehensive coverage of diverse perspectives, facilitating the identification of objects familiar to a wide audience.

2.6.3 Results

Average ratings were computed across the three participant groups for all objects (Table 2.3). Additionally, the proportion of participants from each group who rated an object as three (indicating highest familiarity) was calculated for each object. Twenty-four objects were shortlisted, meeting the criterion of receiving a rating of three from over 90% of participants across all demographic groups. Out of the shortlisted objects, ten objects with the highest ratings across all three participant groups and falling in our inclusion criteria were selected to be used as stimuli in our cognitive tasks. The inclusion criteria ensured that the chosen objects spanned diverse semantic categories and were distinct from each other, avoiding any similarities between them. For example, we omitted objects with similar shapes, such as a bottle and a candle (Figure 2.4) or a spoon and a fork, to prevent additional cognitive effort in stimulus perception. Moreover, we ensured the inclusion of at least one object from each semantic category.

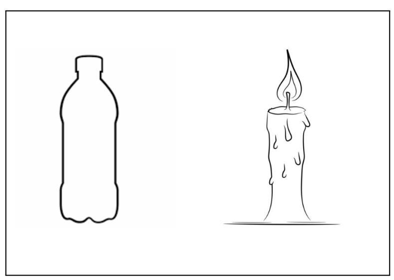


Figure 2.4 An example of objects with similar shapes.

2.6.4 Conclusion

Our study carefully selected ten objects with the highest ratings among participants, ensuring they belonged to diverse semantic categories and lacked similarities between them. This meticulous selection process aimed to optimize participants' cognitive task performance by using easily perceivable stimuli. By adhering to this approach, we expect to preserve the effectiveness of our cognitive tasks in assessing specific cognitive abilities, aligning with the overarching goal of our study.

Table 2.3 List of objects presented for the familiarity study with their average ratings (*min* = 1, *max* = 3) across three participant groups. Note: * denotes a selected object.

Objects	Semantic Category	NIMS Group (n=22)	Housekeeping Staff (n=15)	IIIT Students (n=15)
Bag *	General	3	3	3
Ball	General	2.7	2.7	3
Umbrella *	General	3	3	3
Comb	General	2.7	2.4	3
Key	General	2.9	2.9	3
Lock	General	2.8	2.9	3
Book	General	2.8	2.6	3
Candle *	General	2.8	2.9	3
Specs	General	2.8	3	2.9
Pen/Pencil *	General	3	3	3
Clouds	Nature	2.2	2.2	3
Star *	Nature	3	2.6	2.7
Flower	Nature	2.9	2.9	2.4
Moon	Nature	2.4	1.4	3
Sun	Nature	2.9	2.5	3
Scissors *	Kitchen	2.9	2.8	3
Knife	Kitchen	2.9	2.6	3
Bottle	Kitchen	3	3	3
Spoon	Kitchen	3	3	3
Fork	Kitchen	2.7	2.7	3
Gas Stove	Kitchen	2.8	2.8	2.7
Light Bulb	Electronics	2.9	2.8	3
Television	Electronics	2.9	2.9	3
Telephone	Electronics	2.9	2.8	3
Fan *	Electronics	3	2.9	3
Refrigerator *	Electronics	2.9	3	3
Remote	Electronics	2.6	2.9	3
Mobile Phone *	Electronics	3	3	3
Chair	Furniture	3	2.8	3
Table	Furniture	2.9	2.9	3
Clock *	Furniture	2.9	2.8	3
Bed	Furniture	2.9	2.8	3

2.7 Validation Study

2.7.1 Introduction

The linguistic and educational diversity of India poses significant hurdles in developing normative data, even for widely accepted cognitive tests such as the N-back and SART. These challenges are escalated among the illiterate population, who lack metalinguistic training and visuosymbolic representation [84]. Previous studies have highlighted the challenges faced by individuals with reading difficulties in tasks like the N-back, emphasizing the limitations of existing cognitive tests designed primarily for English-proficient populations [76].

This study seeks to address the above-mentioned issue by developing language-independent variation of the N-back and SART tasks by replacing the alphanumeric characters with images of everyday objects, such as ”bag,” ”fan,” and ”bottle” as stimuli. This modification aims to make these cognitive tasks accessible to a linguistically diverse population, especially individuals with low literacy or illiteracy. Notably, most previous studies have primarily involved educated young adults, making our work distinctive in its inclusion of the economically and educationally diverse Indian population.

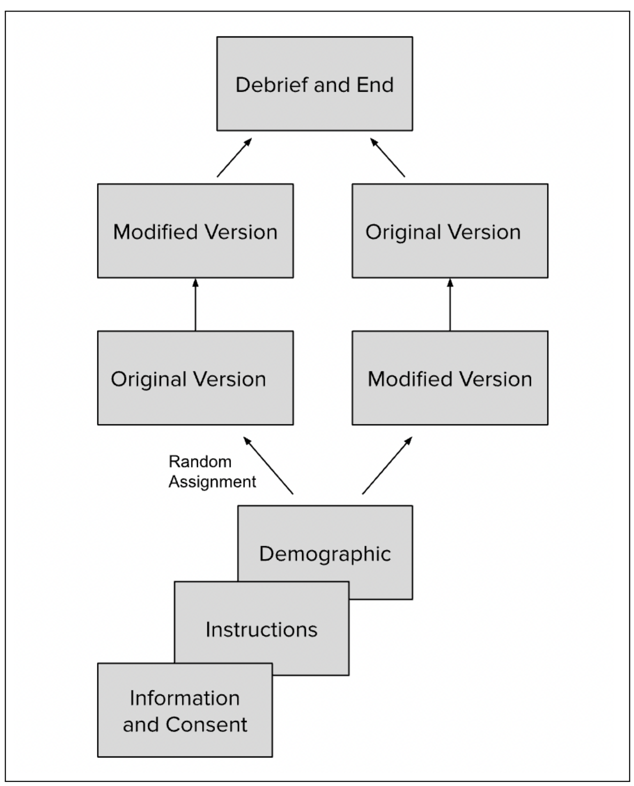


Figure 2.5 Schematic Representation of flow of a session

2.7.2 Methods

A total of 60 participants were recruited for the N-back (*age: Median* = 22, *IQR* = 11) and SART (*age: Median* = 22, *IQR* = 10) tasks, with 30 individuals separately for N-back and SART task. Further, 30 participants in each test comprised college-going students ($n = 20$) with a minimum Bachelor's degree either pursuing or completed and the housekeeping staff ($n = 10$) with a wide spectrum of educational qualifications, ranging from primary level education ($n = 4$) to post-graduation ($n = 2$). The latter group included individuals with limited proficiency in the English language, primarily readers or speakers of Telugu or Hindi, but tested familiarity with basic reading of English letters and digits.

We conducted a stimuli familiarity study to create a language-independent version of the tasks (refer to section 2.6). The top 10 objects (such as "bag", "fan", and "candle") with the highest familiarity ratings across all participants were selected for use in the modified tasks. Participants completed two sets of tasks: one using the original version (with English alphabets for N-back and digits for SART) and another with a new version replacing letters and digits with images of common daily objects (Figure 2.5). This assignment was completely random for every participant. A single set took 10-15 minutes for N-back and 8-10 minutes for SART. Participants were individually administered in a quiet setting with comfortable seating arrangements as per their convenience. Task details for both tasks are explained below:

N-back task: Both versions included 0, 1, 2 and 3-back conditions, each with 50 trials divided into two blocks. In both versions, stimuli were presented for 2000 milliseconds, and the participant was supposed to press the "SPACEBAR" key as soon as they identified the target (Figure 2.6). Participant's response key and reaction time were recorded.

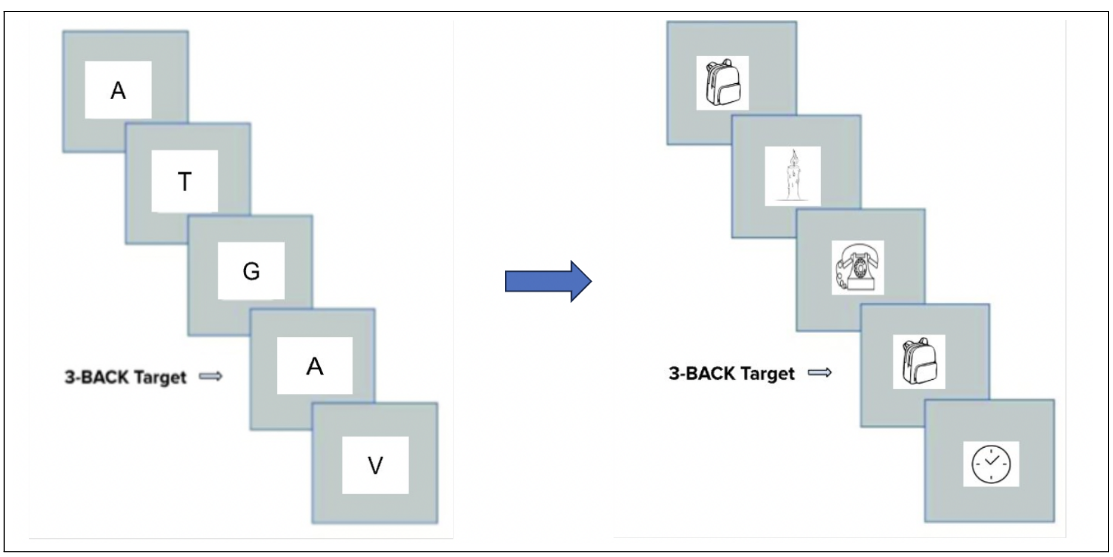


Figure 2.6 Adaptation introduced from Traditional (left) to Updated (right) version for N-back task

Performance metrics included total accuracy expressed as a percentage. Total response time was recorded in milliseconds. Additionally, D-Prime scores were calculated to assess participants' sensitivity to task demands and performance efficiency.

SART task: Both versions of the SART task consisted of a total of 225 trials, comprising 200 GO trials and 25 NO-GO trials, distributed across five blocks to minimize participant fatigue. As the stimulus changed from digits to objects, the stimulus duration varied between 250 milliseconds and 450 milliseconds. The chosen duration was determined through a participant comfort test and was consistent across both versions (Figure 2.7). Participant's response key and reaction time were recorded.

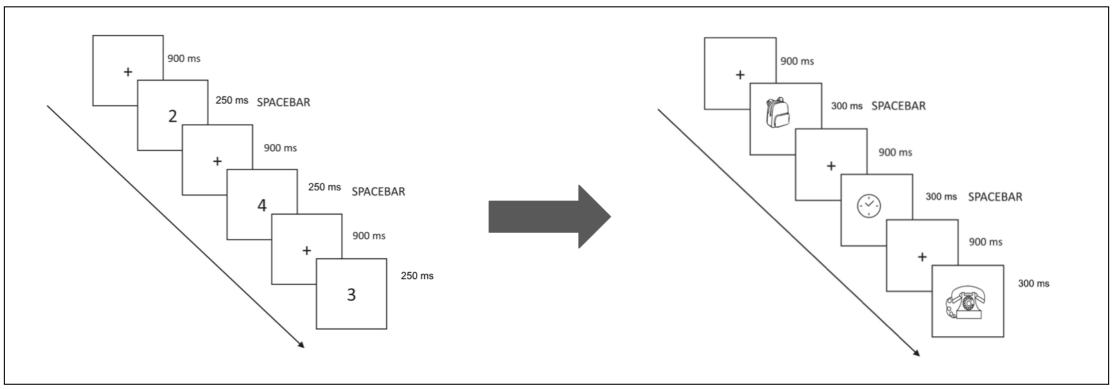


Figure 2.7 Adaptation introduced from Traditional (left) to Updated (right) version for SART

Performance assessment encompassed total accuracy in percentage and individual accuracies for GO and NOGO trials. Commission errors (false alarms) and omission errors (false negatives or misses) were indicators of vigilance performance. Reaction times (milliseconds) were recorded to determine average response times across all trials and individually for GO and NO-GO trials.

2.7.3 Results

We employed the Mann-Whitney test to compare participants' cognitive performance across the two task versions. Due to the lack of significant differences between the two task versions, we failed to reject the null hypothesis (Table 2.4 and 2.5).

Spearman's correlation analysis was used to measure the relationship between the original and modified versions for both tasks. The results showed a positive correlation between the original and modified versions of the N-back task and the SART task (Figure 2.8, 2.9 and 2.10).

Table 2.4 Cognitive scores (Median (IQR)) for Nback for letters and objects category.

Cognitive Task	Letters/Digits	Objects	P-value	Rank-Biserial Correlation
0-back Score	100(0)	100(1.5)	0.777	0.033
1-back Score	98(4)	98(6)	0.487	0.102
2-back Score	96(16.5)	96(23)	0.834	0.032
3-back Score	84(17)	84(19)	0.778	-0.043
0-back D-Prime	4.65(0)	4.65(0.32)	0.853	0.022
1-back D-Prime	4.22(1.2)	3.86(1.5)	0.487	0.103
2-back D-Prime	3.67(2.2)	3.45(3.2)	0.870	0.026
3-back D-Prime	2.06(1.5)	2.07(1.6)	0.824	-0.034
0-back RT (ms)	675.5(302.5)	632.7(290.2)	0.247	-0.320
1-back RT (ms)	667.9(192.3)	685.3(300.8)	0.971	-0.020
2-back RT (ms)	915.4(316.7)	941.4(246.4)	0.190	-0.360
3-back RT (ms)	1079.6(236.2)	984.1(227.1)	0.684	-0.120

Table 2.5 Cognitive scores (Median (IQR)) for SART for letters and objects category.

Cognitive Task	Letters/Digits	Objects	P-value	Rank-Biserial Correlation
Overall RT	304.23(66.31)	304.81(79.38)	0.959	0.009
GO RT	324.18(75.75)	322.47(91.37)	0.820	0.036
NOGO RT	122.39(70.52)	146.41(100.42)	0.398	-0.129
Overall Accuracy	90.67(4.77)	84.77(5.22)	0.636	0.072
GO Accuracy	95.0(5.37)	95.0(4.50)	0.947	-0.011
NOGO Accuracy	64.0(28.0)	60.0(34.0)	0.458	0.112
Commission Errors	36.0(28.0)	40.0(34.0)	0.458	-0.112
Omission Errors	5.0(5.37)	5.0(4.50)	0.947	0.011

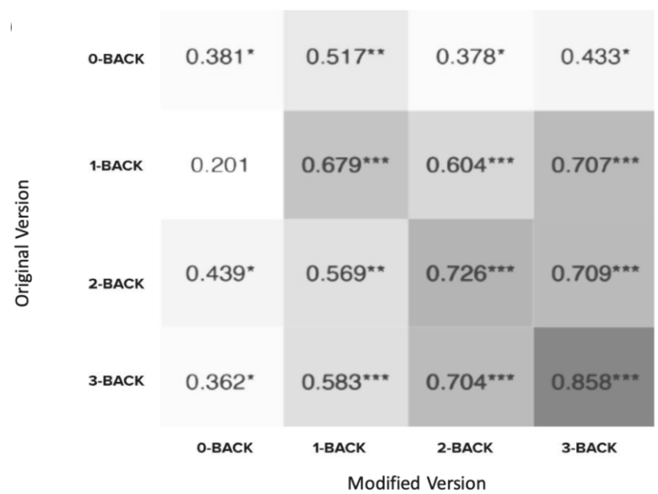


Figure 2.8 Spearman's coefficient (ρ) between the D-Prime Scores of Original (Letters) and Modified (Objects) version of the N-back task. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

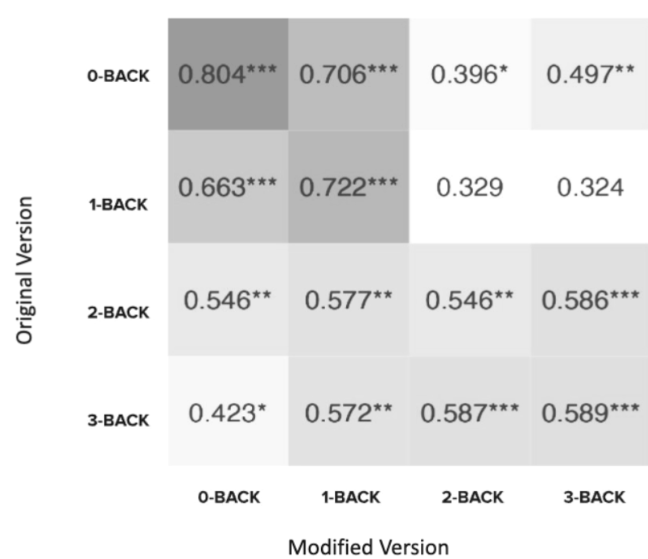


Figure 2.9 Spearman's coefficient (ρ) between the Average RT of Original (Letters) and Modified (Objects) version of the N-back task. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

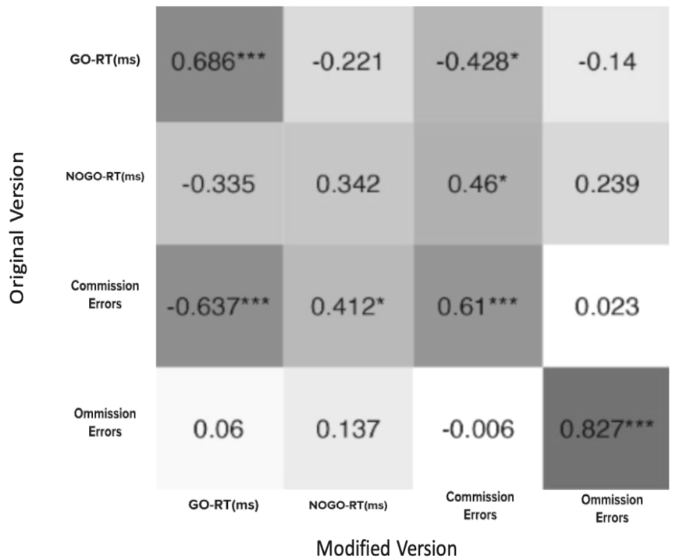


Figure 2.10 Spearman's coefficient (ρ) between the Original (Digits) and Modified (Objects) version of the SART task. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

2.7.4 Conclusion

The results suggest that regardless of literacy or socio-economic status, the new task version yields results akin to the original, exhibiting its suitability. The inclusion of everyday objects as stimuli has an advantage over other language-dependent stimuli since the participants can perceive the displayed object in their preferred language and prepare their responses accordingly. Thus, the shift from letters and digits to highly familiar objects paves the way for enhanced accessibility of these tasks to a wider audience. No difference in the traditional and modified versions of n-back and SART also supports the adaptation of these tests for more inclusive cognitive assessments.

Chapter 3

Psychological Well-being of SLE Patients: A Comprehensive Examination of Distress and Quality of Life

This chapter focuses on the psychological well-being of SLE patients. SLE is a chronic autoimmune disease affecting various organs, leading to emotion and mood regulation issues. Despite the increasing prevalence of SLE globally and in India, the neuropsychological data remain underrepresented. This chapter investigates the psychological health and quality of life among Indian SLE patients through self-reported questionnaires on depression, general anxiety, trait anxiety, stress, and quality of life. Results indicate the prevalence of psychological health issues in SLE patients along with reduced quality of life scores. A significant correlation between disease severity and patients' psychological health is observed, highlighting SLE's profound impact. Moreover, disease severity correlates with the quality of life domains, highlighting the association with other crucial factors like physical well-being, societal relations, and environmental conditions in their daily functioning. Additionally, the significant correlation between psychological distress and quality of life scores emphasizes the multifaceted nature of mental health, which is influenced by a combination of factors.

3.1 Introduction

Systemic Lupus Erythematosus (SLE) stands as a multifaceted autoimmune disease known for its diverse clinical manifestations, impacting mainly women and specific ethnic groups [43]. Its dynamic nature yields a variable disease trajectory, necessitating continual monitoring to spot emerging or recurrent organ and systemic involvements. SLE can affect various organs, including the central nervous system (CNS), adding layers of complexity to its diagnosis and treatment. The involvement of CNS may lead to neuropsychiatric disorders like strokes or seizures, defining a subtype known as neuropsychiatric systemic lupus erythematosus (NPSLE). However, diagnosing NPSLE remains challenging [85], with reported prevalence rates ranging widely from 6% to 91% [36]. The symptoms of NPSLE can vary in severity and may include acute cognitive impairments, anxiety, mood disorders, psychosis, and disruptions in emotion and mood regulation [15–17].

Neuropsychiatric disorders affect around 70% of SLE patients [86], with depression and anxiety as the most frequently reported psychological issues among SLE patients. Research indicates that the prevalence of depression and anxiety is twice as high in SLE patients compared to healthy adults [87,88]. A meta-analysis reported a wide range of prevalence for depression (2% to 91.7%) and anxiety (4% to 85%) across different studies [89]. Importantly, psychological disorders are not limited to NPSLE patients; even those without apparent neuropsychiatric symptoms (non-NPSLE) experience psychological distress [19]. Depression and anxiety significantly impact the mental well-being of SLE patients and are closely linked to a diminished quality of life [89]. Stress further compounds these challenges, serving as a trigger for disease flares and exacerbating symptoms [22, 90]. Studies have identified stress as a predictive factor for fatigue, depression, and pain among individuals with SLE, underscoring its significant role in contributing to multiple symptoms [23]. In sum, the high prevalence of depression and anxiety in SLE patients, irrespective of overt neuropsychiatric symptoms, and their strong association with stress and diminished quality of life emphasize the heterogeneous nature of this disease.

The increasing prevalence of SLE [36] underscores a growing concern regarding its impact on patient's mental well-being. SLE's prevalence and incidence rates vary widely, ranging from 3.2 to 3000 per 100,000 and 0.3 to 8.7 per 100,000 individuals, respectively [39, 41]. Despite this variability, there is a notable lack of comprehensive psychological data, especially from diverse populations in Asia and Africa. Existing assessments and studies predominantly focus on Western populations, neglecting representation from ethnically, culturally, and linguistically diverse regions. Additionally, the absence of standardized neuropsychiatric screening tools, limited neuropsychiatric professionals [55], and inadequate digital health resources in Low and Middle-Income countries (LMICs) like India further constrain neuropsychological assessments. The social stigma surrounding mental health, socio-economic and educational challenges, and cultural beliefs about psychological issues contribute to this complex scenario, impeding effective monitoring and support for SLE patients. This critical gap underscores the urgent need to explore the psychological dimensions of SLE among the Indian population. Our study aims to establish psychological baselines for Indian SLE patients using standardized assessments across various psychological domains.

3.2 Methods

3.2.1 Participants

In this study, a total of a hundred and two individuals (F = 92%, median age *Mdn* = 25 years, *IQR* = 9.75 years) diagnosed with systemic lupus erythematosus (SLE) and meeting the 2012 SLE classification criteria [91] were enrolled as Cases. The inclusion criteria specified that participants must be adults aged between 18 and 45 years to minimize the potential impact of age-related cognitive impairments, and they were required to have completed a minimum of ten years of education. Out of a hundred and two cases, eighty-eight outpatients and fourteen admitted SLE cases volunteered for the study. The doctors confirmed the diagnosis as SLE and provided the required medical records with widely used measures: Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (SLICC/ACR-DI) [92, 93]. SLEDAI-2K accounts for organ system involvement and symptoms over the preceding 30 days from the assessment date [92]. Higher SLEDAI-2K scores are indicative of heightened disease activity. The SLEDAI-2K score ranged between 0 and 23 (*Mdn* = 3), and the SLICC/ACR damage index (SDI) ranged between 0 and 5 (*Mdn* = 0). Thirty-three SLE patients were identified as NP+ according to the BILAG scale [94]. Clinical characteristics of the patients are given in Table 3.1.

Table 3.1 Clinical Characteristics of SLE Patients (n=102)

SLE Categories	No. of Patients	Percentage
NPSLE (BILAG)	33	32.3%
Acute Cutaneous	63	61.7%
Chronic Cutaneous	21	20.5%
Oral or nasal ulcers	52	50.9%
Non- scarring alopecia	61	59.8%
Arthritis	72	70.5%
Serositis	24	23.5%
Renal	48	47%
Neurologic	23	22.5%
Hemolyticanemia	13	12.7%
Leukopenia	65	63.7%
Thrombocytopenia	47	46%
ANA	93	91.1%
Anti-dsDNA	63	61.7%
Anti-Sm	23	22.5%
Antiphospholoid antibodies	12	11.7%
Low complement	79	77.4%

A total of a hundred and five demographically matched healthy individuals were recruited in two control groups using the convenience sampling method. First, CG (caregivers) (n = 52, F = 54%, median age *Mdn* = 24.5 years, and *IQR* = 12.5 years) comprised family members or friends of the patients (not necessarily SLE patients) who were accompanying them to the same hospital. Second, CS (college students) (n = 53, F = 58%, median age *Mdn* = 21 years, *IQR*= 3 years), consisted of college-going young adults. The exclusion criteria for control groups encompassed any personal history of autoimmune diseases or any other medical condition that could affect cognition. The rationale behind choosing these particular control groups was to ensure diversity in culture, language, and socioeconomic backgrounds. Participants were not given any monetary compensation for the same.

3.2.2 Procedure

Each session began with an assessment of inclusion and exclusion criteria, followed by the consent form. Detailed information about the study and the voluntary nature of participation, including the right to withdraw at any point without repercussions, was provided. Upon obtaining participant consent, the assessment commenced with a detailed demographic and health questionnaire. The psychological well-being questionnaires were randomly assigned to the participants to control the order effect. The experiment was performed in a quiet room, and the session lasted approximately 15 to 20 minutes. The study received approval from the respective institutional research ethics review board committees (IRB).

3.2.3 Materials and Measures

The assessment comprised five distinct psychological questionnaires, including the Patient Health Questionnaire (PHQ-9) for depression, the Generalized Anxiety Disorder Assessment (GAD-7) for general anxiety, the Perceived Stress Scale (PSS-4) for stress, the Spielberger State-Trait Anxiety Inventory (STAI-T) for trait anxiety, and the World Health Organization Quality of Life Brief Assessment (WHOQOL-BREF), collectively aimed to offer a holistic evaluation of various psychological domains crucial for understanding the psychological health and quality of life among individuals navigating the complexities of SLE.

3.2.3.1 Patient Health Questionnaire - 9:

The PHQ-9 questionnaire was designed as a concise, 9-item self-reported tool to evaluate an individual's experience of depression within the preceding two weeks, including the assessment date [95]. Each item of the questionnaire examined whether the respondent had been affected by specific problems or symptoms associated with depression during this time frame. Participants were instructed to carefully review each query and rate their experience on a 4-point scale: 0 indicating *not at all* and 3 signifying *nearly every day*. The scores for each response were tallied by summing the ratings across all nine items, resulting in a total score that spans a range from 0 to 27. The cut-off scores were 5, 10, 15 and 20 for mild, moderate, moderately severe and severe depression, respectively.

3.2.3.2 Generalized Anxiety Disorder - 7:

The GAD-7 questionnaire is an effective 7-item, self-reported tool designed to gauge an individual's generalized anxiety within the preceding two weeks, including the assessment date [96]. Like PHQ-9, GAD also used a similar frequency scale. The scale ranged from 0 = *not at all*, indicating the absence of the symptom, to 3 = *nearly every day*, denoting frequent occurrence. Upon completing the assessment, scores for each response were tabulated by summing the ratings across all seven items. This cumulative score represents a comprehensive evaluation of the severity of general anxiety experienced by the individual during the specified time frame, spanning a scoring range from 0 to 21. The cut-off scores were 5, 10 and 15 for mild, moderate and severe anxiety levels, respectively.

3.2.3.3 Perceived Stress Scale - 4:

In this study, we adopted the 4-item variant of PSS-10 due to time constraints and its user-friendly nature [97]. This abbreviated questionnaire aimed to assess the frequency of feelings experienced by participants over the preceding month. Participants were instructed to carefully consider each question and rate their responses on a 5-point scale, ranging from 0 = *never* to 4 = *very often*. For evaluation, the scores for the first and fourth questions are directly added, while responses for the second and third questions are reversed on the scale before summation. This method yields a total score ranging from 0 to 16, where higher scores signify elevated levels of perceived stress. A score greater than or equal to 6 was considered the cut-off for high stress.

3.2.3.4 State-Trait Anxiety Inventory - Trait:

STAI is a widely used tool for assessing both state and trait anxiety. This study used a concise version consisting of 5 questions for each state and trait anxiety [98]. In our assessment, we only utilized the segment designed to measure trait anxiety. Participants were instructed to devote sufficient time to contemplate each question and respond based on their general feelings. Participants expressed the extent to which each statement reflected their overall emotional state, using a 4-point scale ranging from 1 = *not at all* to 4 = *very much so*. Scores were computed by aggregating the responses across the 5 trait anxiety-related items, resulting in a total score ranging between 5 and 20. A score greater than or equal to 14 was considered the cut-off for high-trait anxiety.

3.2.3.5 World Health Organization Quality of Life:

The WHOQOL-BREF questionnaire, a shorter version of the original 100-item assessment, was chosen for our study to ensure efficiency and participant convenience. It comprised 26 items incorporating inquiries about the participant's feelings in the past two weeks, using varying response scales distributed across different domains [99]. Questions prompt individuals to evaluate 'how much', 'how completely',

’how often’, ’how good’, or ’how satisfied’ they experienced aspects of their life [100]. With items evaluating physical health, psychological well-being, social relationships, and environmental aspects, this abbreviated version offers a more streamlined yet comprehensive assessment of an individual’s quality of life.

3.3 Statistical Analysis

Power analysis was performed using G*Power version 3.1.9.6 [101] to calculate the minimum sample size necessary to test the study hypothesis. According to the results, N = 159 was the minimum sample size needed for a one-way ANOVA (fixed effects, omnibus) including three participant groups in order to achieve 80% power for detecting a medium effect at a significant threshold of α =.05. As a result, the selected sample size (*n* = 53 for each participant group) is sufficient for validating the study hypothesis. Moreover, we collected a nearly doubled sample size for the SLE patient population (*n* = 102) to analyze disease heterogeneity using more robust techniques like cluster analysis.

Statistical Analysis was performed using the JASP version 0.17.3 [102]. We utilised the chi-squared test to analyse the demographics of the three participant groups. We conducted a multivariate analysis to assess the psychological test scores (GAD, PHQ, PSS and STAI-T) as dependent variables across the three participant groups: Cases, CG, and CS. Adequate sample sizes ensured that the number of participants in each group exceeded the number of dependent variables, and the independence of observations was also guaranteed. Box’M test yielded a p = 0.724, suggesting no violation of the multivariate homogeneity of variance. Additionally, multivariate normality was assessed using the Shapiro-Wilk test, adhering to the normalcy assumption (p = 0.052). Further, multicollinearity revealed moderate correlations among the psychological test scores, ranging from $\rho = 0.295$ to $\rho = 0.646$, meeting the assumption criteria. Adhering to the assumptions of homogeneity, multivariate normality, and multicollinearity, MANOVA was employed to analyze the psychological health scores, namely PHQ-9, GAD-7, STAI-T, and PSS-4, across the three participant groups [103]. However, a deviation from normalcy ($p < 0.05$) was observed for the individual psychological health scores. Consequently, we employed the Kruskal-Wallis test for the post-hoc analysis, followed by Dunn’s test with Bonferroni correction for the pair-wise comparisons. Similarly, the WHOQOL data violated the normalcy assumption and led us to choose the Kruskal-Wallis test to identify specific psychological domains that affected the QOL across three participant groups. Further, Dunn’s post-hoc test with Bonferroni correction was used for pair-wise comparisons.

In addition to the comparative analysis, Spearman’s correlational analysis explored the relationships between psychological health, quality of life, and disease severity. Moreover, we conducted a cluster analysis to identify the heterogeneity within our SLE patient population. We opted for the K-Means algorithm with four psychological test scores as parameters for defining our clusters. Mann-Whitney or chi-squared tests were used to compare the clusters based on the variable types. Finally, we determined the trends of psychological well-being among Indian SLE patients by calculating standard deviations

(SD) for each patient's scores, using the mean and SD of both the health control groups as benchmarks for comparison.

3.4 Results

The results section is structured into three main segments. The first segment focuses on the demographics of the participant groups. Secondly, the ”Psychological Well-being Score” section compares the psychological health (depression, anxiety and stress) and quality of life scores among the SLE patients and the control groups. Lastly, the ”SLE Disease and Psychological Well-being” section delves into the heterogeneity associated with the psychological well-being of SLE patients through correlational and cluster analysis. It explores the relationship between disease severity, psychological health, and quality of life in SLE patients. Additionally, cluster analysis was used to visualize the differences in the distribution of the patient population based on their psychological health scores. Finally, we determine the trends of psychological well-being in our patient population.

3.4.1 Demographics

Table 3.2 Demographics of participant groups: Cases (n=102), CG (n=52), CS (n=53)

Demographics	Cases	CG	CS
Gender, female	92.1%	53.8%	58.4%
Education			
Secondary	18.6%	9.6%	0%
Higher Secondary	37.2%	38.4%	71.6%
Tertiary	39.2%	46.1%	24.5%
Post Graduation	4.9%	5.7%	3.7%
Occupation			
Working	15.6%	38.4%	0%
Non-working	54.9%	17.3%	0%
Students	29.4%	44.2%	100%

The analysis focused on categorical demographic variables, including gender, education, occupation, family income, and self-income (Table 3.2). Cases were demographically matched with the CG group based on education and family income, representing the Indian rural population. To capture additional diversity, we included a second control group comprising urban college-going young adults. This group differed from the SLE cases and CG in factors such as education and family income, providing additional insights into the impact of these variables on cognitive assessment. Notably, a significant proportion of the SLE cases comprised women working as homemakers. Consequently, differences emerged between the Cases and the healthy controls, particularly concerning gender, occupation, and self-income.

3.4.2 Psychological Well-being Score

3.4.2.1 Psychological health score:

Psychological health scores (Appendix Table 5.3) showed a significant difference between the participant groups *(F (2,204) = 2.599; p = 0.009; *Wilk's* Λ = 0.904). Kruskal-Wallis was performed separately on the psychological test scores for the three groups of participants. Significant differences were noted in GAD, PSS, and STAI-T scores (Table 3.3). Dunn's test with Bonferroni correction in the pair-wise analysis between the three participant groups with the GAD, PSS and STAI-T revealed a significantly higher level of anxiety (p = 0.019) and stress (p = 0.019) in SLE patients compared to the caregivers (Figure 3.1). However, no significant difference was observed between the participant groups in terms of trait anxiety (STAI-T scores). Moreover, no significant difference was found between the SLE patients and the college students (Figure 3.1).

Table 3.3 Psychological health and WHOQOL scores (*Mean* and *SD*), and Kruskal Wallis statistical values for the three groups, Cases, caregivers (CG), and college students (CS).

Variables	Cases (n=102)	CG (n=52)	CS (n=53)	Kruskal Wallis H(df)
PHQ (Depression)	8.1(5.7)	6.7(5.0)	8.5(5.0)	3.2(2)
GAD (General Anxiety)	8.3(5.2)	5.9(4.4)	7.9(4.5)	7.9(2)*
PSS (Stress)	7.9(2.6)	6.5(2.5)	7.8(3.2)	7.9(2)*
STAI-T (Trait Anxiety)	11.8(4.1)	10.2(3.6)	10.3(3.4)	7.2(2)*
WHOQOL Physical	23.6(4.7)	27.8(4.4)	27.9(4.5)	37.4(2)***
WHOQOL Psychological	18.4(4.6)	22.0(4.5)	21.0(4.6)	20.7(2)***
WHOQOL Social	10.1(2.4)	11.4(2.1)	11.2(2.1)	10.8(2)**
WHOQOL Environmental	22.2(5.0)	24.9(5.0)	27.6(4.7)	35.8(2)***

Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

The raincloud plot demonstrates the raw distribution of participants across the three groups and helps us visualize the distribution [104] of psychological health issues (Figure 3.1) along with the mean difference between the three groups. The descriptive statistics show that around 40% of cases and college students reported moderate to severe anxiety (GAD score >= 10). However, only 30% caregivers reported a similar experience. Similarly, high trait anxiety (STAI-T score >= 14) was observed in 41% of cases but only 19% of college students and 17% of caregivers. In contrast, high stress (PSS score >= 6) was prevalent in more than 50% of all three participant groups, with 83% of cases, 75% of caregivers, and 73% of college students reported experiencing it in the last month. In the case of depression, an almost equal level of depressive state was observed across the groups, with 35% of cases, 28% caregivers and 37% of college students reporting moderate to severe (PHQ score >= 10) depression symptoms.

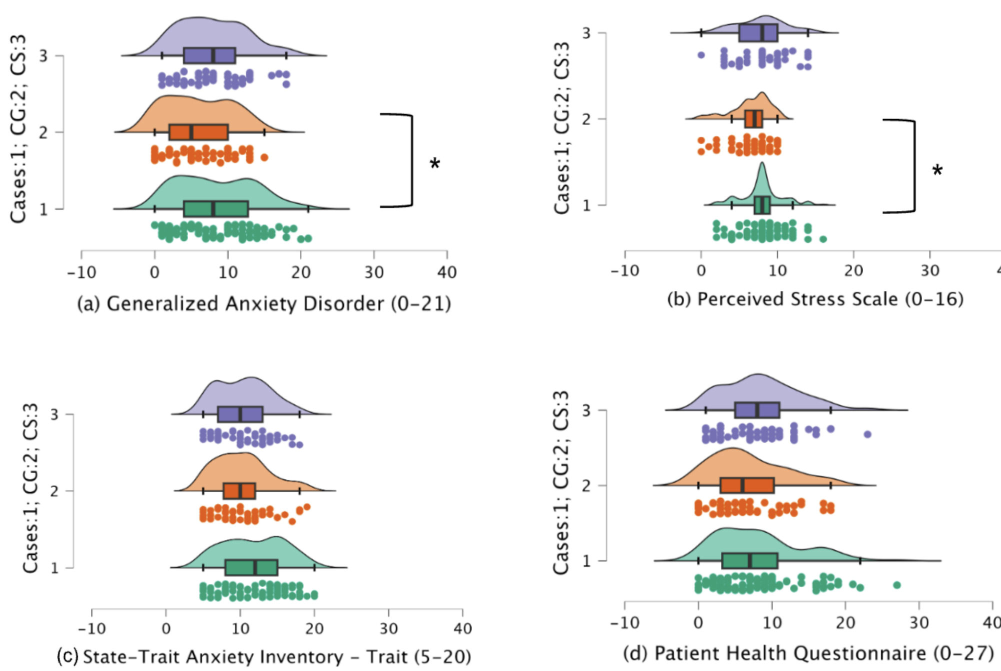


Figure 3.1 Raincloud plot depicting scores for (a) Generalized Anxiety Disorder (GAD-7) (b) Perceived Stress Scale (PSS-4) (c) State-Trait Anxiety Inventory - Trait (STAI-T) (d) Patient Health Questionnaire (PHQ-9) for the three groups: Cases, caregivers (CG) and college students (CS). Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

3.4.2.2 WHO quality of life score:

The results revealed considerable differences in quality of life scores across all domains: physical, psychological, social, and environmental (Table 3.3). Post-hoc analysis showed significantly lower quality of life scores for SLE patients compared to control groups in the physical, psychological, social and environmental domains (Figure 3.2). Additionally, college students had significantly better environmental domain scores than caregivers.

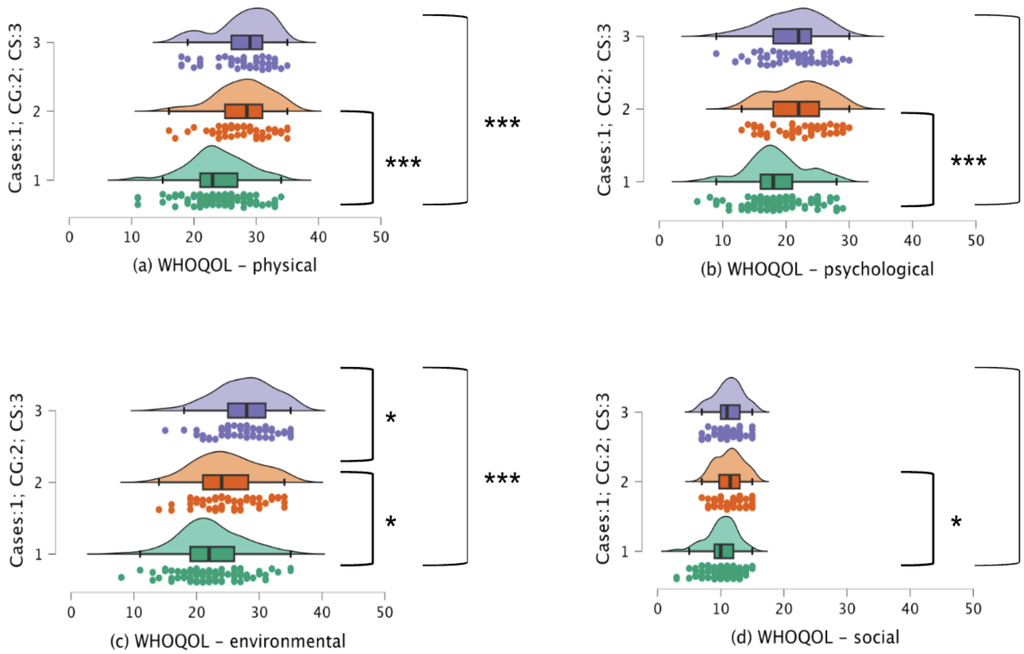


Figure 3.2 Raincloud plot for Quality of Life Scores for (a) physical (b) psychological (c) environmental (d) social for the three groups: Cases, caregivers (CG) and college students (CS). Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

3.4.3 SLE disease and Psychological Well-being

3.4.3.1 Correlational Analysis

Spearman's correlational analysis was conducted to examine the impact of disease severity on the psychological health and quality of life of SLE patients. Disease severity was quantified using SLEDAI-2K (mentioned in the Participants section under Methods). We observed a weak but significant positive correlation of SLEDAI-2K with GAD and PSS scores (Figure 3.3), suggesting a higher level of stress and anxiety in patients with increased disease severity. However, the SLEDAI-2K score showed a weak but significant negative correlation with social and environmental domains of quality of life experiences by SLE patients.

Further, we examined the relationship between the quality of life scores and the psychological well-being of the patients. There was a consistent negative correlation of all four domains of quality of life (physical, psychological, social and environmental) with the diverse psychological domains (GAD, PHQ, PSS and STAI-T) assessed in our study (Figure 3.3). A strong and significant negative correlation was observed for the physical domain of QOL with anxiety (GAD) and depression (PHQ). The psychological QOL domain also showed a strong correlation with depression (PHQ), trait anxiety (STAI-T), and general anxiety (GAD), indicating the construct validity of these measures.

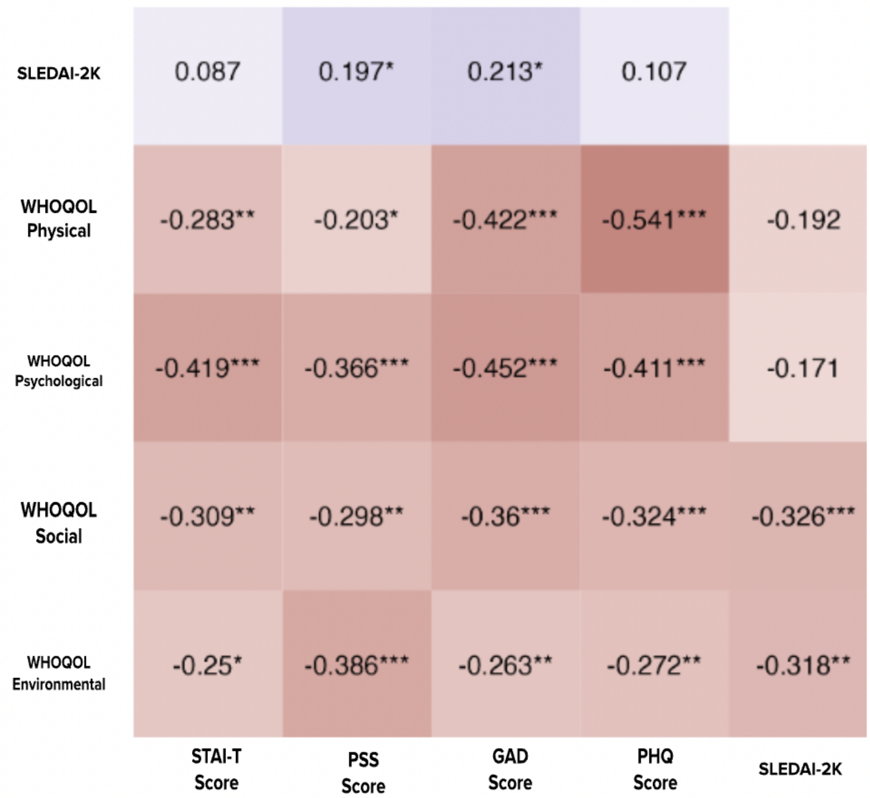


Figure 3.3 Spearman's coefficient (ρ) between psychological health, WHOQOL domains and SLEDAI-2K in SLE Patients. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

3.4.3.2 Cluster Analysis

We utilized the K-Means algorithm to categorize clusters based on four psychological scores: STAI-T, PHQ-9, GAD-7 and PSS-4. Two clusters were identified with a combined silhouette score of 0.380 (*Cluster 1* = 0.338 and *Cluster 2* = 0.410). Silhouette scores range from -1 to +1, with higher scores indicating better clustering quality [105]. Figure 3.4 shows the t-SNE plot for visualizing the cluster memberships [106]. Because of the violation of multivariate homogeneity ($p < 0.001$) and multivariate normality (p = 0.005) assumptions, we used the non-parametric Mann-Whitney test instead of multivariate analysis (MANOVA) to compare the two clusters. Results revealed that Cluster 1 exhibited poorer psychological health than Cluster 2, evidenced by their higher scores across all psychological tests (Figure 3.5).

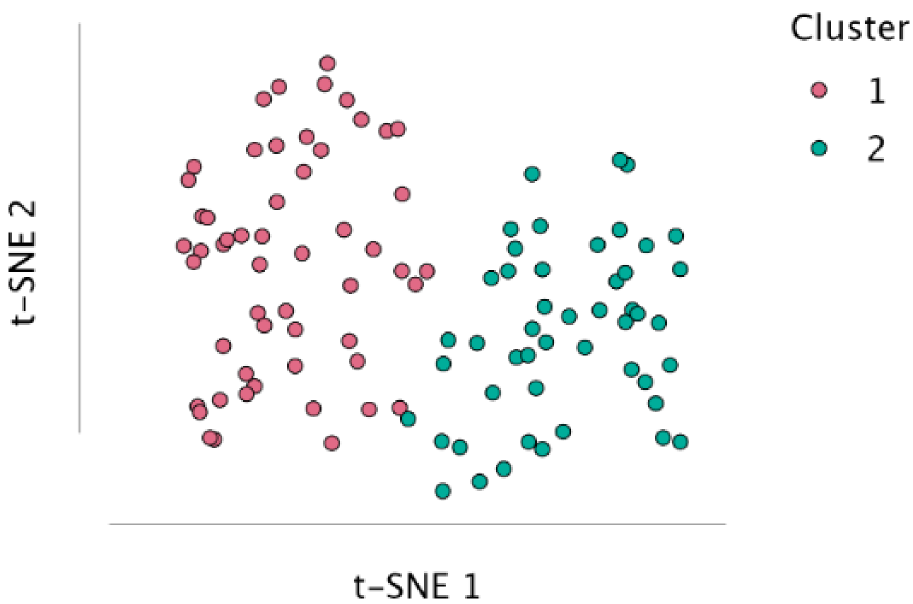


Figure 3.4 t-SNE plot for clusters. Each coloured dot represents one sample in its respective cluster.

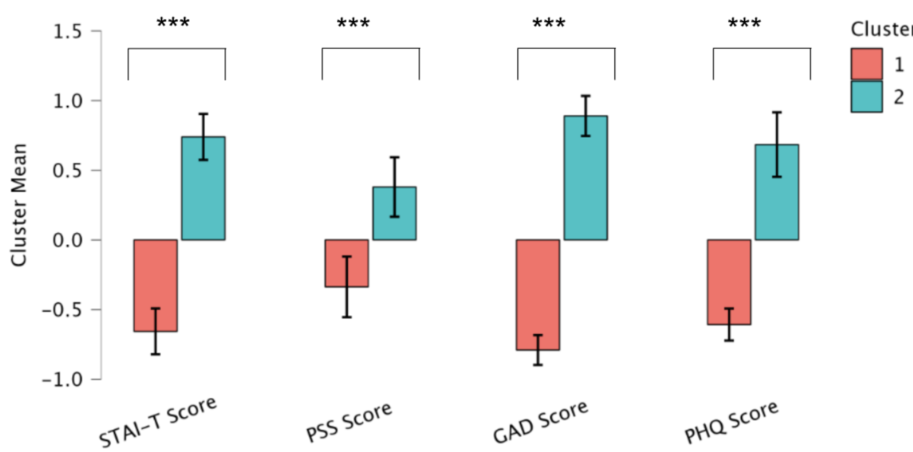


Figure 3.5 Cluster Means for the psychological health scores of the two clusters. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

Additionally, Cluster 1 showed lower WHOQOL scores in physical, psychological, social and environmental domains than Cluster 2 (Table 3.4). Demographically, Cluster 1 differed from Cluster 2 in terms of age (p = 0.001) and occupation ($p < 0.001$), with Cluster 1 mainly comprising older women who were predominantly unemployed. Clinically, Clusters 1 and 2 did not differ in the disease severity score (SLEDAI-2K), damage index (SDI), and neuropsychiatric involvement (NPSLE or non-NPSLE based on BILAG scores).

Table 3.4 Age and WHOQOL scores [Median (IQR)] for clusters and effect size (Rank Biserial Correlation of Mann-Whitney test) for comparison between clusters.

Variables	Cluster 1 (n = 48)	Cluster 2 (n = 54)	Effect Size
Age	29.0 (7.25)	23.0 (8.0)	0.369**
WHOQOL Physical	23.0 (6.0)	25.5 (6.75)	-0.436***
WHOQOL Psychological	16.5 (3.0)	20.0 (7.0)	-0.513***
WHOQOL Social	10.0 (3.25)	11.0 (2.0)	-0.410***
WHOQOL Environmental	21.0 (5.0)	23.0 (6.75)	-0.272*

Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

3.4.3.3 Trends of Psychological Well-being in Indian SLE Patients

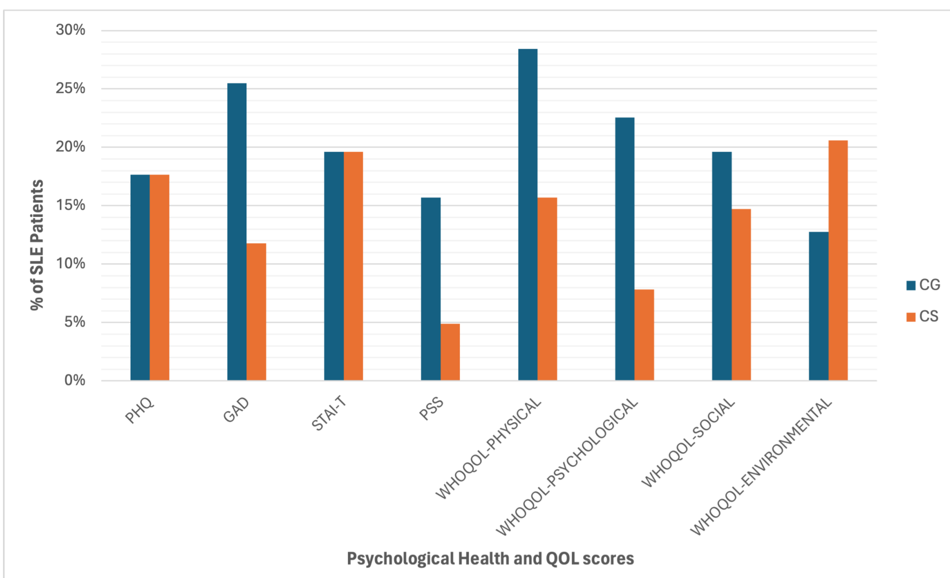


Figure 3.6 Prevalence of psychological health issues in SLE patients compared to the healthy control groups. The percentage of SLE patients with a psychological health issue is calculated using a threshold of 1.5 SD below the means of the healthy control groups.

We determined the standard deviation (SD) for each patient's psychological and quality of life scores by comparing them to the mean and standard deviation of two control groups: CG and CS. Our criterion for identifying psychological health deterioration was set at a threshold of greater than 1.5 standard deviations below the mean of the control groups. Figure 3.6 illustrates the percentage of SLE patients exhibiting psychological decline in each domain based on this threshold. Compared to CG, 45% of SLE patients displayed symptoms for at least one of the four psychological disorders (depression, general anxiety, state anxiety and stress) evaluated in our study. In comparison, when compared to CS, 34% of SLE patients exhibited symptoms for at least one of these disorders.

3.5 Discussion

The study examines the relationship between individuals' psychological well-being and quality of life experiences with autoimmune disease, namely SLE. The comprehensive evaluation between the three participant groups (SLE cases, caregivers and college students) revealed elevated levels of stress and anxiety compounded with reduced quality of life (WHOQOL) experiences across all the domains (physical, psychological, social and environmental) in SLE cases compared to the control groups, CG and CS. Additionally, the disease severity exhibited a positive correlation with stress and anxiety, whereas a negative correlation was observed with the quality of social engagement and environment. This elaborated web of correlations suggests that factors contributing to mental health extend beyond psychological factors, incorporating aspects related to physical well-being, social interactions, and the environment. Further, results from cluster analysis highlight the heterogeneity associated with the psychological well-being of SLE patients, revealing distinct distributions within the patient population based on psychological health scores. Despite observing a significant relationship between psychological well-being and SLE disease, the pervasive presence of psychological distress symptoms was evident across the groups (Figure 3.1 and Figure 3.2) in the current study. The results are discussed in light of previous findings and emerging trends in mental health worldwide and in India.

3.5.1 Psychological Health and SLE

Our study highlights the high prevalence of self-reported psychological health issues in SLE patients, with more than 30% of the cases reporting experiences of depression, anxiety and stress [107, 108]. Further, the association between disease severity and psychological health aligns with the previous findings and poses a serious concern regarding the cases' well-being and its association with their daily activities [108].

When compared to their healthy counterparts, SLE patients reported higher levels of anxiety and stress. [107,109]. However, the current study fails to observe a significant difference between depressive symptoms across cases and healthy controls as seen previously [17]. One explanation could be the widespread nature of psychological health issues among young adults. The dispersion of psychological disorder symptoms across the groups can be seen in the raincloud plot (Figure 3.1). Recent studies [20, 21] have raised concern regarding increasing trends of psychological distress among young adults. In India, it is suggested that nearly 15% of the population grapples with mental health issues at least once in their lifetime [20]. The pervasive prevalence of mental health issues among young adults weakens the recognition of SLE-induced psychological health concerns among patients and, in turn, impedes timely intervention.

3.5.2 Psychological Health and Quality of Life with SLE

Mental health is a complex, multifactorial issue. Among various factors, quality of life significantly correlates with an individual's mental well-being [110], particularly when someone is grappling with an autoimmune disease. SLE cases' poorer quality of life experiences across all domains suggest impaired everyday functioning. The compounding effect can be observed with disease severity, notably with the diminished quality of social engagement, an essential requirement for healthy living.

We also observed an association between psychological health and quality of life, suggesting that the better the quality of life is, the better the psychological health will be. By considering factors beyond psychological well-being, such as environmental, social, and physical influences, we gained a more holistic understanding of the overall well-being of SLE patients. This holistic perspective is crucial, as it acknowledges the diverse factors that contribute to the mental health of individuals with SLE. Thus, focusing solely on psychological well-being might overlook the broader context within which these individuals navigate their daily lives. Hence, our study contributes to a more thorough outlook on the mental well-being of individuals with SLE. The current findings recommend the inclusion of neuropsychiatric evaluation of SLE patients as part of regular primary health care practice.

3.5.3 Heterogeneity in Psychological Health of SLE Patients

Results from cluster analysis revealed a clear distinction between the two clusters regarding their psychological well-being. Notably, these variations were evident through self-reported evaluations on depression, general anxiety, trait anxiety, and stress levels, with one cluster exhibiting elevated psychological symptoms. This cluster predominantly consisted of an older demographic that was largely unemployed. This observation resonates with prior studies emphasizing the impact of unemployment on mental health, particularly in regions with limited economic development [111]. Additionally, individuals in this cluster reported lower quality of life across physical, psychological, social, and environmental domains, aligning with previous research linking quality of life to the mental health of SLE patients [112]. These insights highlight the heterogeneous nature of psychological well-being among SLE patients, emphasizing the role of various demographic factors and advocating for targeted research to uncover the multifaceted contributors to this complexity.

However, our study did not find significant differences in clinical factors such as disease severity (SLEDAI-2K) or prevalence of neuropsychiatric manifestations (BILAG scores) between the identified clusters. This finding was unexpected, especially considering the known association between mental health disorders and central nervous system (CNS) involvement in SLE patients [112]. The lack of association between BILAG scores and psychological health scores raises questions about the adequacy of current measures in assessing the nature of neuropsychiatric manifestations in SLE. These results prompt a critical examination of existing medical protocols for NPSLE classification, which may not fully capture the complexity and nuances of neuropsychiatric conditions lacking factors such as temporal relationships of NPSLE to SLE diagnosis and disease severity as mentioned in previous studies [85]. Therefore, our study recommends the use of a multi-dimensional frequency-based psychological state assessment that enables a more comprehensive outlook of a patient than currently widely used medical protocols. While current NPSLE medical protocols provide valuable information on the occurrence of neuropsychiatric incidents, they may fall short in offering insights into the frequency, quality, and severity of these occurrences. Therefore, there is a pressing need for an integrated examination that goes beyond binary categorizations and explores the intricate details of the patient experience. To further enrich our understanding, more investigations should delve into the heterogeneity associated with SLE and its nuanced impact on various psychological and quality-of-life domains.

3.5.4 Psychological Health of Indian SLE Patients

The trends revealed the presence of at least one psychological symptom in 45% of SLE patients compared to the caregivers. This underscores the substantial presence of psychological symptoms within the patient cohort when compared to the healthy control group matched for age, education, and socio-economic background. These findings are consistent with prior studies in India, which report similar trends in prevalence rates with depression and anxiety being the major symptoms [113,114]. Conversely, when compared against college students as the baseline, only 34% of the patients showed signs of at least one psychological symptom. This highlights the prevalence of mental health issues in young adults [20, 115]. Hence, it is important to consider factors such as socioeconomic background and education when defining a healthy control group beyond merely the absence of the disease. Despite an increasing number of studies focusing on the Indian population, there remains a significant gap in well-defined normative baseline data. Future research endeavours are crucial to establish comprehensive baseline data to facilitate more accurate comparisons in this field.

3.5.5 Conclusion and Future Direction

In conclusion, our study is one of the first studies to provide a comprehensive assessment of the psychological health and quality of life among Indian SLE patients. Results reveal the presence of psychological symptoms among the SLE patient cohort when compared to their healthy counterparts. We explored the associations between psychological health, quality of life, disease factors and demographic factors. However, given the heterogeneous nature of SLE, a more nuanced analysis of the widespread psychological health issues through approaches like network or regression analysis is needed. Moreover, it's crucial to acknowledge the diverse spectrum of neuropsychiatric symptoms in SLE, ranging from emotional disorders to significant cognitive impairments. Previous studies have highlighted cognitive deficiencies across various domains critical for daily functioning, emphasizing the importance of investigating SLE's impact on cognitive health alongside psychological well-being [24–27]. Incorporating cognitive health assessments will provide a more comprehensive understanding of the intricate relationship between cognitive and psychological health in individuals with SLE.

Chapter 4

Cognitive Assessment of SLE Patients

This chapter focuses on the cognitive health of SLE patients. SLE is a chronic autoimmune disease affecting multiple organs, leading to cognitive health issues. Despite the increasing prevalence of SLE globally and in India, the neuropsychological data remain underrepresented. Existing assessments are primarily designed for English-speaking populations and lack standardization across linguistically and culturally diverse groups, limiting their effectiveness in diverse Indian communities. We aim to address this gap by employing a comprehensive digital language-independent neuropsychological battery. This battery was tailored to evaluate critical cognitive domains such as working memory, vigilance/sustained attention, language proficiency, alertness, orientation, and executive functioning among Indian SLE patients. The results revealed a notable prevalence of cognitive health issues among SLE patients compared to healthy individuals, particularly concerning working memory, language skills, sustained attention, executive functioning, and processing speed. Furthermore, the study highlighted more severe cognitive dysfunction among Neuropsychiatric SLE (NPSLE) patients compared to those without evident neuropsychiatric symptoms. Additionally, we identified two clusters based on the distribution of patients by their cognitive performance. The underperforming cluster was characterized by higher disease activity and lower education levels, highlighting the heterogeneity associated with this disease group.

4.1 Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by a diverse range of clinical presentations [2]. It affects various organs, including the central nervous system (CNS), leading to a subtype known as Neuropsychiatric systemic lupus erythematosus (NPSLE), characterized by severe neurological and psychiatric symptoms. The reported prevalence of NPSLE varies significantly, ranging from 6% to 91% [36]. Cognitive dysfunction is a recognized component of SLE, acknowledged as one of the five psychiatric syndromes by the American College of Rheumatology [16]. This dysfunction can affect patients both with and without overt central nervous system involvement, with prevalence rates ranging from 20% to 80% [16]. In a 2006 study, the prevalence of cognitive impairment was reported to be 12% in the sample [116]. However, a more recent study in 2023 reported a significantly higher prevalence of 70% [30]. The wide variation in prevalence rates can be attributed to several factors such as the absence of consensus in screening tools, the inherent heterogeneity within patient population groups, and variations in study procedures [15].

The spectrum of cognitive impairments associated with SLE spans across crucial domains essential for daily functioning. These encompass deficits in executive functioning [27], visuospatial attention [24, 27], sustained attention [25], working memory [26, 27], language proficiency [25, 26], verbal memory [24, 25] and psychomotor speed [24] [24–27]. Notably, studies have highlighted that the most affected domains include working memory, executive functioning, and attention [30, 69]. Moreover, neuroimaging studies have revealed associations between microstructural white matter abnormalities and these cognitive impairments [32]. Specifically, impaired working memory has been linked to left frontal lobe white-matter atrophy in SLE patients [33]. Additionally, slower processing speed, observed in both NPSLE and non-NPSLE individuals, has shown a strong correlation with white matter integrity [34]. Given the profound impact of cognitive dysfunction on SLE patients, there is an urgent need for heightened recognition and incorporation of cognitive assessment within clinical settings.

The widely used assessments for assessing cognitive impairments include the Stroop test, Montreal Cognitive Assessment (MoCA), Wechsler Adult Intelligence (WAIS-R), etc [57–59]. However, these assessments are predominantly designed in English and necessitate a certain level of language proficiency, which poses challenges for diverse populations like those in India with varied linguistic, cultural, and educational backgrounds. While efforts have been made to translate the tests into different languages [81], the vast linguistic diversity in countries like India makes comprehensive translation and standardization across all languages a challenging task. Furthermore, ensuring the ongoing validity and reliability of these translated tests requires periodic updates, adding to the complexity. Another limitation of traditional neuropsychological assessments is their reliance on paper-pencil formats, which demand skilled professionals for administration. This poses a significant barrier, especially in Low and Middle-Income countries like India, where there is a shortage of qualified professionals to cater to a large population [55]. Embracing digital solutions not only alleviates this burden but also allows for integrating advanced technologies such as eye tracking and functional imaging. The transition to digital platforms is an ongoing endeavour aimed at enhancing user experience and accessibility in cognitive testing [65, 66].

The current challenges in cognitive assessments for linguistically and culturally diverse populations highlight a notable scarcity of neuropsychological data that accurately represents these diverse groups. This scarcity is particularly evident in India, where the prevalence of SLE is increasing (3.2 per 100,000 individuals [39]). India ranks among the top countries globally for newly diagnosed SLE cases, following China, with significant numbers in both female and male populations [41]. Despite the escalating prevalence and incidences of SLE, there exists a significant dearth of comprehensive neuropsychological data tailored to Indian populations. While studies have focused on the Asian population [45], India's linguistically and culturally diverse population remains underrepresented. This study specifically targets the neuropsychological testing of Indian SLE patients, aiming to fill the substantial gap in characterizing SLE related cognitive dysfunctions for this demographic. Our approach involves using a language-independent digital neuropsychological test battery to address the challenges posed by linguistic diversity. This battery includes customized versions of standardized tests tailored to suit the cultural and linguistic context of the Indian population.

4.2 Method

4.2.1 Participants

In this study, a total of a hundred and two individuals (F = 92%, median age *Mdn* = 25 years, *IQR* = 9.75 years) diagnosed with systemic lupus erythematosus (SLE) and meeting the 2012 SLE classification criteria [91] were enrolled as Cases. The inclusion criteria specified that participants must be adults aged between 18 and 45 years to minimize the potential impact of age-related cognitive impairments, and they were required to have completed a minimum of ten years of education. Out of a hundred and two cases, eighty-eight outpatients and fourteen admitted SLE cases volunteered for the study. The doctors confirmed the diagnosis as SLE and provided the required medical records with widely used measures: Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics American College of Rheumatology Damage Index (SLICC/ACR-DI) [92, 93]. SLEDAI-2K accounts for organ system involvement and symptoms over the preceding 30 days from the assessment date [92]. Higher SLEDAI-2K scores are indicative of heightened disease activity. The SLEDAI-2K score ranged between 0 and 23 (*Mdn* = 3), and the SLICC/ACR damage index (SDI) ranged between 0 and 5 (*Mdn* = 0). Thirty-three SLE patients were identified as NP+ according to the BILAG scale [94]. Clinical characteristics of the patients are given in Table 4.1.

A total of a hundred and five demographically matched healthy individuals were recruited in two control groups using the convenience sampling method. First, CG (caregivers) (n = 52, F = 54%, median age *Mdn* = 24.5 years, and *IQR* = 12.5 years) comprised family members or friends of the patients (not necessarily SLE patients) who were accompanying them to the same hospital. Second, CS (college students) (n = 53, F = 58%, median age *Mdn* = 21 years, *IQR*= 3 years), consisted of college-going young adults. The exclusion criteria for control groups encompassed any personal history of autoimmune diseases or any other medical condition that could affect cognition. All the participants had normal or corrected-to-normal vision. The rationale behind choosing these particular control groups was to ensure diversity in culture, language, and socio-economic backgrounds.

Table 4.1 Clinical Characteristics of SLE Patients (n=102)

SLE Categories	No. of Patients	Percentage
NPSLE (BILAG)	33	32.3%
Acute Cutaneous	63	61.7%
Chronic Cutaneous	21	20.5%
Oral or nasal ulcers	52	50.9%
Non- scarring alopecia	61	59.8%
Arthritis	72	70.5%
Serositis	24	23.5%
Renal	48	47%
Neurologic	23	22.5%
Hemolyticanemia	13	12.7%
Leukopenia	65	63.7%
Thrombocytopenia	47	46%
ANA	93	91.1%
Anti-dsDNA	63	61.7%
Anti-Sm	23	22.5%
Antiphospholoid antibodies	12	11.7%
Low complement	79	77.4%

4.2.2 Procedure

The study received approval from the respective institutional research ethics review board committees (IRB). Volunteers meeting the predefined inclusion and exclusion criteria were recruited for participation in the study. Prior to their involvement, participants were provided with detailed information about the study objectives, procedures, potential comfort and discomfort, data privacy and their voluntary participation rights. They were explicitly informed about their right to withdraw from the study at any point without facing any repercussions. Monetary compensation was not offered to participants to maintain the integrity of voluntary participation. Upon understanding the terms and conditions of the study, participants were required to sign an informed consent form if they agreed to participate. Following participant consent, each individual completed a detailed demographic and health questionnaire. Subsequently, participants were randomly assigned to either of the cognitive assessment tasks to minimize order effects. Every participant underwent the assessment in a quiet setting. The duration of each participant's involvement ranged between 40 to 60 minutes. Although the intention was to conduct the entire assessment in a single session, accommodations were made to split the assessment into two sessions if preferred by the participant due to fatigue or convenience concerns.

4.3 Cognitive Assessment

Our study employed the standard Montreal Cognitive Assessment (MoCA) and four modified computer-based cognitive tasks: N-back task for working memory, Sustained Attention to Response task (SART) for continuous performance, Picture Naming for language proficiency, and Attention Network task (ANT) for assessing alertness, orientation, and executive control. Developed and implemented via the Psychopy interface, these tasks meticulously captured participant responses and reaction times, comprehensively evaluating diverse cognitive abilities. Task details and performance metrics have been explained below.

4.3.1 Montreal Cognitive Assessment

MoCA is a widely recognized screening tool employed to assess individuals' mild cognitive impairment (MCI) [57]. It is a paper-pencil test which includes cognitive domains such as visuospatial and executive functioning, naming, memory, attention, language, abstraction, and orientation. In this study, MoCA serves as a fundamental component of our cognitive assessment battery, employed as a standard tool against which we validate the results obtained from other detailed cognitive assessments.

Performance metrics include a total score out of 30. Further, individual scores are calculated for the above-mentioned cognitive domains, with maximum scores for visuospatial/executive function being 5, picture naming being 3, memory (delayed recall) being 5, attention and orientation being 6 each, language being 3, abstraction being 2, summing up to a total of 30.

4.3.2 N-Back Task

The N-back working memory task stands as a widely employed paradigm to assess working memory [117]. The task included a sequential presentation of stimuli on a computer screen, prompting participants to press the "SPACEBAR" key upon encountering the target stimulus. There were 3 conditions: 0-back, 1-back and 2-back, presented randomly. For the 0-back condition, the target stimulus was shown at the start of the condition block, and participants were expected to press the key whenever they encountered the same stimulus in the upcoming sequence. For the 1-back condition, a stimulus was considered a target if it was the same as the preceding stimulus (one trial back). Similarly, for the 2-back condition, the target was the stimulus same as shown two trials back.

Each condition comprised two blocks featuring 25 images, including 8 target and 17 non-target stimuli, amounting to a total of 50 images with a 33% target ratio. Stimuli were presented for 2000 ms, allowing responses within a 2500 ms window, followed by fixation of 1000 ms (Figure 4.1). Participants received a practice trial before encountering each condition for the first time, ensuring familiarity with task requirements. Short breaks between blocks were permitted at the participant's convenience.

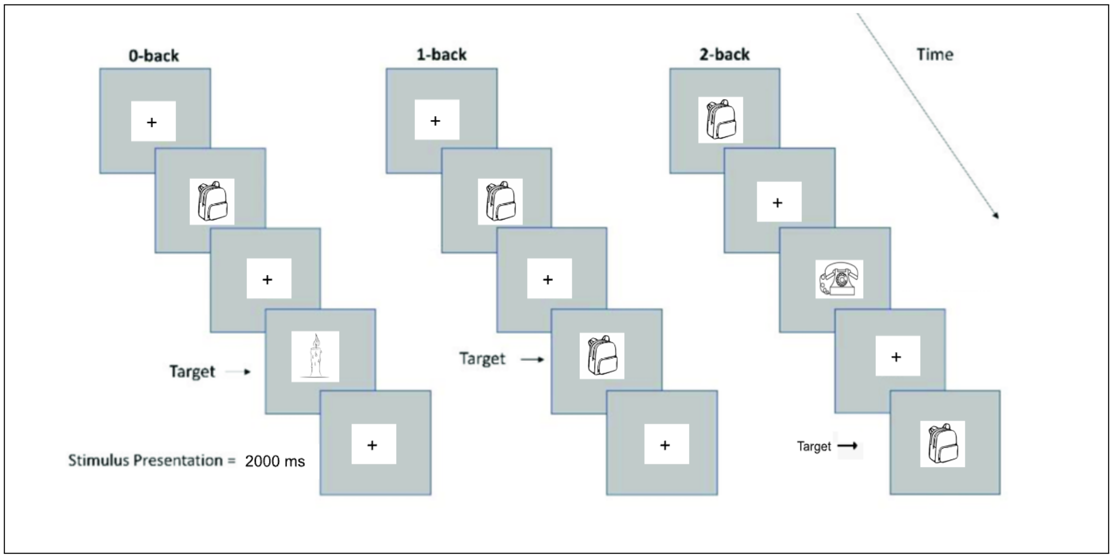


Figure 4.1 Schematic Representation of the N-back task

In line with efforts to minimize language-related biases, traditional n-back was modified to use daily-life objects such as furniture items, electronics, and kitchen appliances as stimuli instead of English alphabets. This modification aimed to mitigate potential cognitive impacts related to low English proficiency among participants, ensuring a more culturally and linguistically sensitive assessment.

Performance metrics encompassed total accuracy, hit rate (true positives), miss rate (false negatives), and false alarms (false positives), expressed as percentages. Total response time was recorded in milliseconds. Additionally, D-Prime values were calculated to assess participants' sensitivity to task demands and performance efficiency.

4.3.3 Sustained Attention to Response Task

SART is a prominent tool for assessing vigilance and sustained attention in cognitive evaluations [118]. It assesses participants' ability to maintain focus and inhibit responses over an extended period. In this task, participants were instructed to press the ”SPACEBAR” key when presented with non-target stimuli (GO trials) and to refrain from responding to target stimuli (NO-GO trials) displayed in sequence on a computer screen.

The task comprised 225 trials (200 GO trials and 25 NO-GO trials) distributed across five blocks to minimize participant fatigue. Each block consisted of 40 GO trials and 5 NO-GO trials. Stimuli were presented for 300 ms, followed by a fixation period of 900 ms, resulting in a total inter-stimulus interval of 1200 ms (Figure 4.2). Before the main task, participants underwent a practice block to familiarize themselves with task requirements and stimuli presentation.

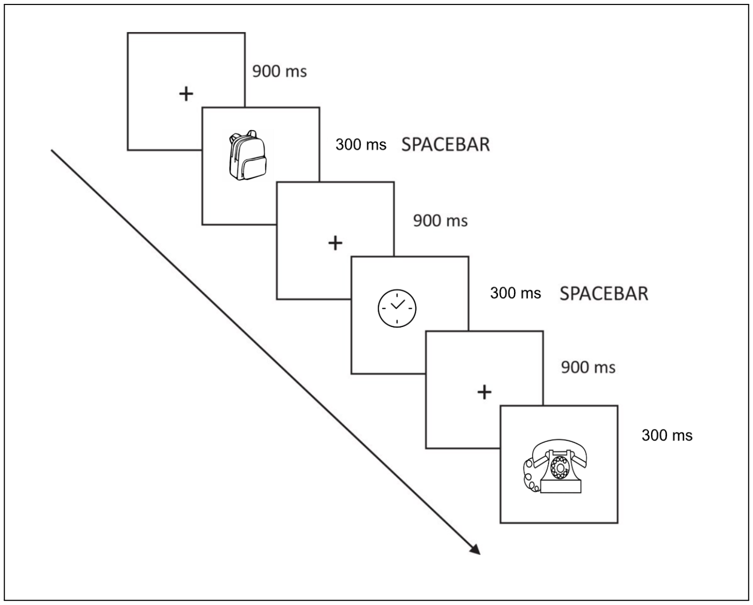


Figure 4.2 Schematic Representation of the SART task

Similar to the N-back task, the traditional SART task was modified to feature daily-life objects as stimuli instead of English digits. This adaptation ensured that participants from diverse linguistic backgrounds could engage with the task effectively, facilitating a more inclusive assessment.

Performance assessment encompassed total accuracy in percentage and individual accuracies for GO and NOGO trials. Commission errors (false alarms) and omission errors (false negatives or misses) served as indicators of vigilance performance, shedding light on participants' ability to sustain attention and inhibit responses appropriately. Reaction times (milliseconds) were recorded to determine average response times across all trials and individually for GO and NO-GO trials.

4.3.4 Attention Network Task

ANT is a pivotal tool for assessing orienting, alerting, and executive control [119]. Participants were instructed to respond to a series of visual stimuli based on the direction of a central stimulus, prompting them to press the corresponding arrow key. The central stimulus is flanked by additional stimuli (flankers), which can exhibit congruency (aligned with the central stimulus), incongruency (opposite direction to the central stimulus), or neutrality (lacking directional indication). Before the visual stimuli appear, participants receive information regarding potential target locations through one of four cue types: no cue, centre cue, double cue, or spatial cue.

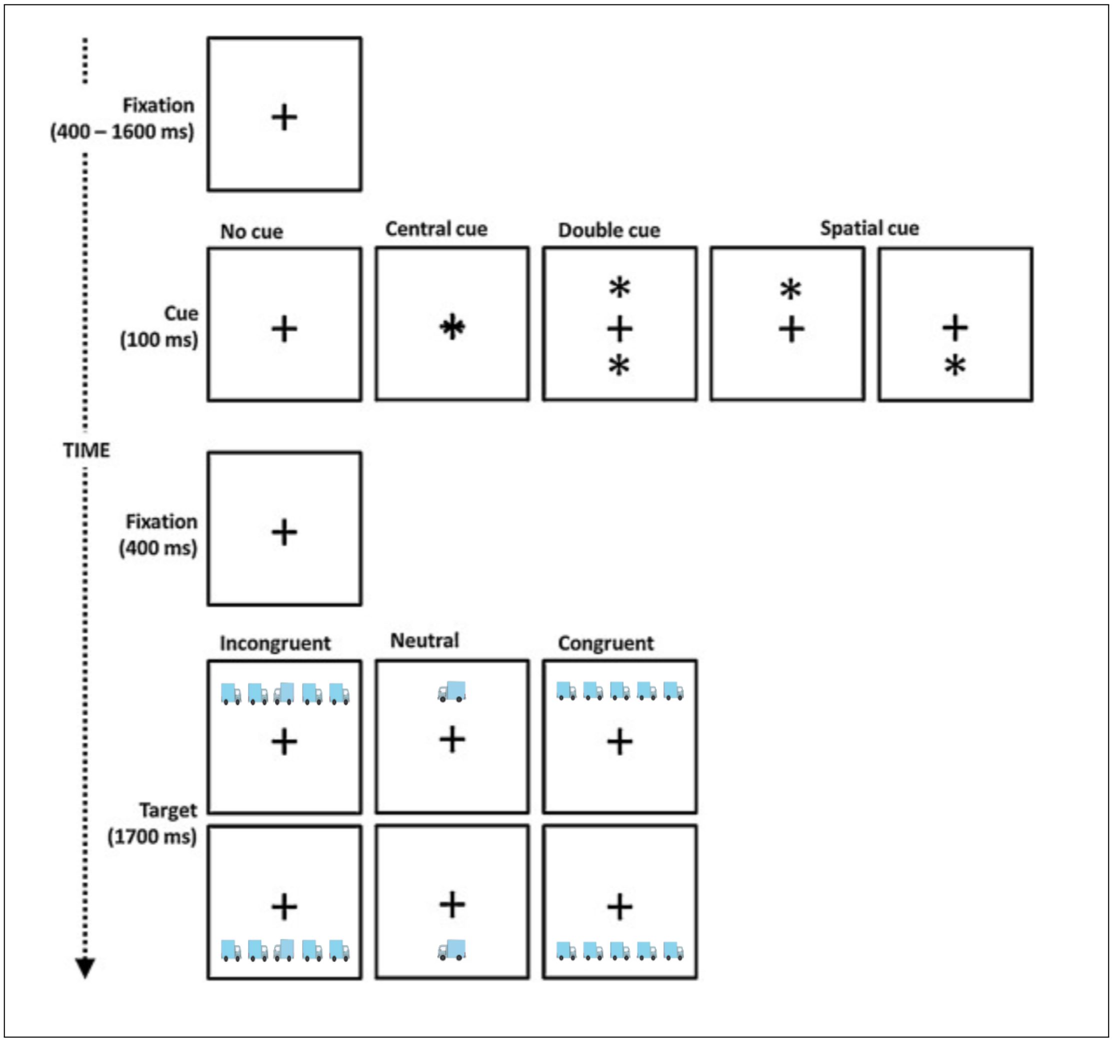


Figure 4.3 Schematic Representation of the ANT task

The main task consisted of 192 trials divided into two blocks, each comprising 96 trials covering four cue conditions, two target locations (top or bottom), two target directions (left or right), and three flanker conditions (congruent, incongruent or neutral), repeated twice. The trial sequence was randomized to minimize order effects, and participants were allowed to take short breaks between blocks. Before the main task, participants underwent a practice block comprising 24 trials to familiarize themselves with task requirements. Each trial started with a fixation period lasting between 400-1600 ms, followed by a 100 ms cue condition. After a brief 400 ms fixation period post the warning cue, participants were presented with the flankers and the target simultaneously, prompting their response. Stimuli were displayed for a maximum duration of 1700 ms before transitioning to the next trial (Figure 4.3).

Our study adapted the traditional ANT employing arrows as stimuli to feature trucks instead. This modification aimed to provide more contextually relevant stimuli and potentially easier to perceive for the specific population under our study, enhancing engagement and task comprehension.

Performance metrics include the three components of the attention network: alertness, orientation and executive functioning. Alertness is calculated as the mean difference between the reaction times and accuracy of the no-cue condition and the double-cue condition. Similarly, orientation is the mean difference between the reaction times and accuracy of the central cue condition and the spatial cue condition. Executive functioning is calculated as the mean difference between the reaction times and accuracy of the incongruent and congruent trials. Moreover, we separately record the reaction times (milliseconds) and accuracy (percentage) for each cue and flanker condition.

4.3.5 Picture Naming Task

The Picture Naming Task serves as a valuable tool for assessing visual perception, semantic knowledge and language fluency among participants [120]. Participants were presented with a series of 21 objects sequentially displayed on a computer screen (Figure 4.4). Their primary task involved identifying and verbally naming each object presented.

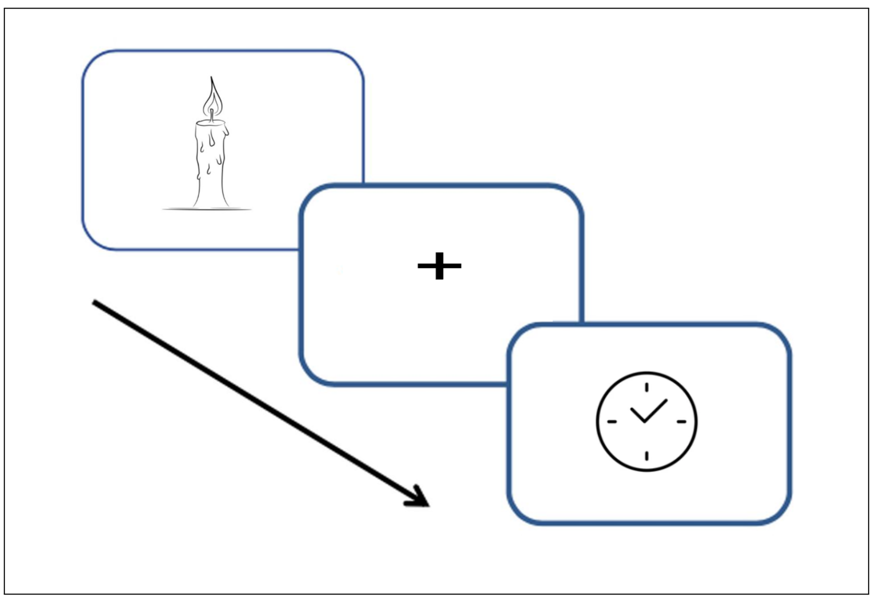


Figure 4.4 Schematic Representation of the Picture Naming task

The objects were drawn from six distinct semantic categories, encompassing everyday-use items, kitchen-related objects, food items like fruits and vegetables, furniture, electronics, and items from nature. Participants were instructed to immediately press the ”SPACEBAR” key upon recalling and verbalizing the name of the object in their preferred language. The objects presented in this task were carefully selected to represent a diverse range of semantic categories, comprehensively assessing participants’ semantic knowledge and language fluency across various domains.

Participants’ reaction times (milliseconds) and accuracy (percentage) in naming the objects were recorded during the task. Reaction times were measured from the presentation of the object to the moment participants pressed the key to indicate their response. Accuracy was measured by the correctness of their responses in their preferred language.

4.4 Statistical Analysis

Power analysis was performed using G*Power version 3.1.9.6 [101] to calculate the minimum sample size necessary to test the study hypothesis. According to the results, N = 159 was the minimum sample size needed for a one-way ANOVA (fixed effects, omnibus) including three participant groups in order to achieve 80% power for detecting a medium effect at a significant threshold of α =.05. As a result, the selected sample size (n = 53 for each participant group) is sufficient for validating the study hypothesis. Moreover, we collected a nearly doubled sample size for the SLE patient population (n = 102) to analyze disease heterogeneity using more robust techniques like cluster analysis.

Statistical Analysis was performed using the JASP version 0.17.3 [102]. We utilised the chi-squared test to analyse the demographics of the three participant groups. Further, we conducted a univariate analysis to assess cognitive performance for each of the cognitive assessments: MoCA, SART, ANT and Picture Naming. Diverse performance metrics (mentioned in the Cognitive Assessment section for each cognitive test) were used as dependent variables across the three independent participant groups: Cases, CG, and CS. However, the Shapiro-Wilk test revealed deviations from normality ($p < 0.05$) for the individual cognitive test metrics. As a result, we opted for the non-parametric Kruskal-Wallis Test as an alternative to one-way ANOVA. Subsequently, we utilized Dunn's test with Bonferroni correction to conduct post-hoc analysis for pair-wise comparisons. For the N-back task comprising three difficulty levels, a 3 (level) x 3 (groups) repeated measures ANOVA appeared to be the appropriate choice. However, the Shapiro-Wilk test indicated deviations from the normality assumption for the data. Consequently, we employed the non-parametric Friedman Test with Bonferroni correction as a suitable alternative. Post-hoc analysis was conducted for pair-wise comparisons within and between groups.

In addition to the comparative analysis between the three participant groups, we analysed the cognitive performance of SLE patients with respect to factors like SLEDAI-2K (disease severity index) and involvement of neuropsychiatric manifestations in patients. We employed the Mann-Whitney test to compare the different groups of SLE patients based on the above-mentioned factors. Moreover, we conducted a cluster analysis to identify the heterogeneity within our SLE patient population. We opted for the K-Means algorithm with seven cognitive parameters for defining our clusters. Mann-Whitney or chi-squared tests were used for comparison between the clusters based on the variable types. Finally, we determined the prevalence of cognitive decline among Indian SLE patients by calculating standard deviations (SD) for each patient's scores, using the mean and SD of both the health control groups as benchmarks for comparison.

4.5 Results

The results section of our study is organized into three key segments. The first segment focuses on the demographics of the participant groups. The second section focuses on the comparative analysis of cognitive performance among the three participant groups: Cases (SLE patients), caregivers (CG), and college students (CS). We present a detailed examination of cognitive metrics, including accuracy, reaction times, error rates, and domain-specific scores across various cognitive tasks. This comparative analysis offers insights into the cognitive functioning differences and similarities among these groups, highlighting any cognitive impairments or strengths associated with SLE. Lastly, we delve deeper into the heterogeneity associated with the cognitive performance of SLE patients. By examining factors related to disease severity and neuropsychiatric involvement, we aim to provide a nuanced understanding of how disease factors may influence cognitive functioning in SLE patients. Further, we use cluster analysis to visualize the differences in the distribution of the patient population based on their cognitive performance, thereby contributing to a comprehensive picture of cognitive functioning in this population. Finally, we determine the prevalence of cognitive decline in our patient population.

4.5.1 Demographics

Table 4.2 Demographics of participant groups: Cases (n=102), CG (n=52), CS (n=53)

Demographics	Cases	CG	CS
Gender, female	92.1%	53.8%	58.4%
Education			
Secondary	18.6%	9.6%	0%
Higher Secondary	37.2%	38.4%	71.6%
Tertiary	39.2%	46.1%	24.5%
Post Graduation	4.9%	5.7%	3.7%
Occupation			
Working	15.6%	38.4%	0%
Non-working	54.9%	17.3%	0%
Students	29.4%	44.2%	100%

The analysis focused on categorical demographic variables, including gender, education, occupation, family income, and self-income (Table 4.2). Cases were demographically matched with the CG group based on education and family income, representing the Indian rural population. To capture additional diversity, we included a second control group comprising urban college-going young adults. This group differed from the SLE cases and CG in factors such as education and family income, providing additional insights into the impact of these variables on cognitive assessment. Notably, a significant proportion of the SLE cases comprised women working as homemakers. Consequently, differences emerged between the Cases and the healthy controls, particularly concerning gender, occupation, and self-income.

4.5.2 Cognitive Functioning among the participant groups

4.5.2.1 N-back Working Memory Task:

The results for this cognitive task are presented in two main sections: Between Subjects and Within Subjects, representing differences among participant groups and within-group performance across load conditions, respectively. Six metrics were evaluated: total accuracy, hit rate, miss rate, false alarms, total reaction time, and d-prime scores (Appendix Table 5.1).

Between Subjects: For the 0-back condition, no difference was found between the participant groups regarding total accuracy, miss rate and false alarms. However, cases exhibited a significantly longer reaction time and lower hit rate and d-prime score than CS. No significant difference was found with the CG group (Table 4.3).

For the 1-back condition, cases displayed significantly poorer accuracy, hit rate, miss rate, false alarms and d-prime scores than CS. Additionally, cases reported a significantly longer reaction time than the control groups (CG and CS). CG had a poor d-prime score compared to CS (Table 4.3).

For the 2-back condition, cases demonstrated significantly weaker performance with respect to accuracy, hit rate, miss rate, false alarms, d-prime score, and reaction time than CS. Compared to CG, cases displayed a higher miss rate and a lower hit rate, resulting in lower accuracy. CS performed better than CG regarding total accuracy, hit rate, miss rate, false alarms and d-prime score (Table 4.3).

Within Subjects: For the Cases group, there was a decrement in accuracy, hit rate, and d-prime score, along with an increase in miss rate, false alarms, and reaction time as the load conditions escalated from 0-back to 2-back. Significant differences were observed between 0-back and 1-back and between 1-back and 2-back conditions.

Similar patterns were observed for the CG and CS groups as the load conditions increased from 1-back to 2-back, although the difference was insignificant between the 0-back and 1-back conditions. In summary, all groups exhibited a memory-related load effect, with SLE patients demonstrating this effect even at lower load conditions in contrast to the healthy control group.

4.5.2.2 Sustained Attention to Response Task:

Results revealed a significant difference in the overall accuracy, omission errors, and reaction time between the three participant groups (Table 4.4). Post-hoc analysis revealed that cases exhibited significantly lower accuracy, followed by CG compared to CS. Omission errors were also significantly higher in cases and CG than in CS. However, no significant difference was found between the accuracy and error rates of Cases and CG. Regarding reaction times, Cases demonstrated significant response latency compared to both control groups (CG and CS). Conversely, no significant difference in reaction times was observed between CG and CS. In summary, Cases exhibited lower accuracy coupled with latency in responses. CG, while displaying lower accuracy, did not exhibit latency in responses. CS emerged as the superior group, showcasing high accuracy and speed in this task compared to the other two groups (Appendix Table 5.2).

4.5.2.3 Attention Network Task:

The assessment of the attentional components across participant groups yielded significant differences in executive functioning (Table 4.4). Post-hoc analysis showed that cases demonstrated a significantly longer reaction time in executive functioning (incongruent reaction time - congruent reaction time) than CS. However, no significant differences were observed among the groups concerning the other two components of attention: alertness and orientation. Individual reaction times across cue and flanker conditions showed significant differences among the participant groups (Table 4.4). Post-hoc analysis revealed that cases exhibited notably longer reaction times than control groups (CG and CS) across all cue and flanker conditions ($p < 0.001$). Additionally, CG displayed significantly longer reaction times than CS ($p < 0.001$). However, no significant differences in accuracy were noted among the three groups, indicating comparable levels of precision in task performance despite differences in reaction times (Appendix Table 5.2).

4.5.2.4 Picture Naming Task:

A significant difference was found in the accuracy and reaction times between the three groups (Table 4.4). Post-hoc analysis showed that Cases had significantly lower accuracy and longer reaction times than the control groups (CG and CS). No difference was found between the control groups (Appendix Table 5.2).

4.5.2.5 Montreal Cognitive Assessment:

Results revealed significant differences in the total score ($p < 0.001$), visuospatial/executive functioning score ($p < 0.001$), picture naming score ($p < 0.001$), attention score ($p < 0.001$), language score ($p < 0.001$) and orientation score ($p = 0.003$) among the participant groups. Post-hoc analysis was done to identify the pair-wise differences. Cases exhibited significantly lower total scores compared to both control groups, indicating pervasive cognitive impairment. Specifically, Cases displayed poorer performance in visuospatial/executive functioning, picture naming, orientation and attention domains than control groups. Moreover, Cases and CG showed lower language domain scores than CS. However, no significant differences among the participant groups were observed in the memory (delayed recall) and abstraction domains.

4.5.3 SLE disease and Cognitive Functioning

This section delves into the heterogeneity associated with cognitive functioning in SLE patients through comparative and cluster analysis. The cognitive performance of SLE patients was analysed with respect to factors like SLEDAI-2K (disease severity index) and involvement of neuropsychiatric manifestations in patients. Furthermore, we categorized SLE patients into clusters based on their cognitive performance to visualize the distribution of these clusters concerning demographics and clinical characteristics. The subsequent sub-sections describe the results based on the above-mentioned factors in detail.

4.5.3.1 Disease severity score - SLEDAI-2K score

Based on the SLEDAI-2K score, SLE patients were divided into two groups. The first group (n = 80) comprised patients with SLEDAI-2K scores ranging from 0 to 5, indicating no to mild activity. The second group (n = 22) comprised patients with scores greater than or equal to 6, indicating moderate to severe activity. Cognitive performance across all cognitive tasks was compared between these two groups. However, the analysis revealed no difference in the performance of the SLE patients on SART, ANT, MoCA and Picture Naming tasks. Interestingly, for the N-back task, no difference was seen in the 0-back condition. For the 1-back condition, the second group (patients with moderate to severe activity) performed poorly than the first group (patients with no to mild activity) on total accuracy ($p = 0.011$), d-prime score ($p = 0.018$) and total reaction time ($p = 0.009$). However, no significant difference was found in the 2-back condition.

4.5.3.2 Neurpsychiatric Involvement (NP+/-)

Another important classification in our study was based on neuropsychiatric involvement using BILAG scores, dividing patients into NP+ (n = 33) and NP- (n = 69) categories. NP+ patients showed a significantly longer reaction time in all cue and flanker conditions in the ANT task ($p < 0.05$) than NP- patients. This group also exhibited a lower hit rate ($p = 0.008$) and false alarm ($p < 0.001$), along with a higher miss rate ($p = 0.008$) in the 2-back condition of the N-back task. Additionally, NP+ patients showed higher omission errors ($p = 0.047$) but lower commission errors ($p = 0.019$) in the SART task than NP-. Surprisingly, we found no significant difference in the MoCA scores between the two groups, except for lower scores in the visuospatial/EC domain ($p = 0.022$) for NP+. Similarly, no significant difference was observed in the Picture Naming task between the NP+ and NP- groups.

Table 4.3 Effect sizes (Cohen's D) for comparing three participant groups on N-back task using Friedman test.

Cognitive Tasks	Cases vs CG	Cases vs CS	CG vs CS
0-back Accuracy (%)	-0.140	-0.468	-0.328
0-back Hit Rate (%)	-0.369	-0.551*	-0.182
0-back Miss Rate (%)	0.357	0.533	0.176
0-back False Alarms (%)	-0.081	0.201	0.281
0-back D-Prime	-0.353	-0.742***	-0.389
0-back RT (ms)	0.463	0.850***	0.388
1-back Accuracy (%)	-0.296	-0.894***	-0.598
1-back Hit Rate (%)	-0.308	-0.880***	-0.571
1-back Miss Rate (%)	0.306	0.725***	0.419
1-back False Alarms (%)	0.154	0.585	0.431
1-back D-Prime	-0.264	-1.294***	-1.030***
1-back RT (ms)	0.773***	1.060***	0.287
2-back Accuracy (%)	-0.564*	-2.331***	-1.767***
2-back Hit Rate (%)	-1.176***	-2.273***	-1.096***
2-back Miss Rate (%)	1.136***	2.195***	1.059***
2-back False Alarms (%)	-0.101	1.312***	1.413***
2-back D-Prime	-0.531	-2.346***	-1.185***
2-back RT (ms)	0.528	0.872***	0.345

Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

Table 4.4 Effect sizes (η^2) for comparing three participant groups on cognitive tasks using Kruskal Wallis test.

Cognitive Tasks	η^2
SART	
Overall Accuracy (%)	0.162***
Commission Error (%)	0.017
Omission Error (%)	0.285***
Overall RT (ms)	0.200***
ANT	
Executive Functioning RT	0.027*
Central Cue RT (ms)	0.498***
Spatial Cue RT (ms)	0.506***
Congruent RT (ms)	0.500***
Incongruent RT (ms)	0.515***
Picture Naming	
Accuracy (%)	0.052**
RT (ms)	0.396***

Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

4.5.3.3 Cluster Analysis

We utilized the K-Means algorithm to categorize clusters based on seven cognitive parameters: 0-back, 1-back, and 2-back d-prime scores (in N-back) for working memory, commission and omission errors (in SART) for continuous task performance, executive functioning accuracy (in ANT), and picture naming accuracy for language proficiency (Figure 4.6). Two clusters were identified with a combined silhouette score of 0.260. Silhouette scores range from -1 to +1, with higher scores indicating better clustering quality [105]. Figure 4.5 shows the t-SNE plot for visualizing the cluster memberships [106].

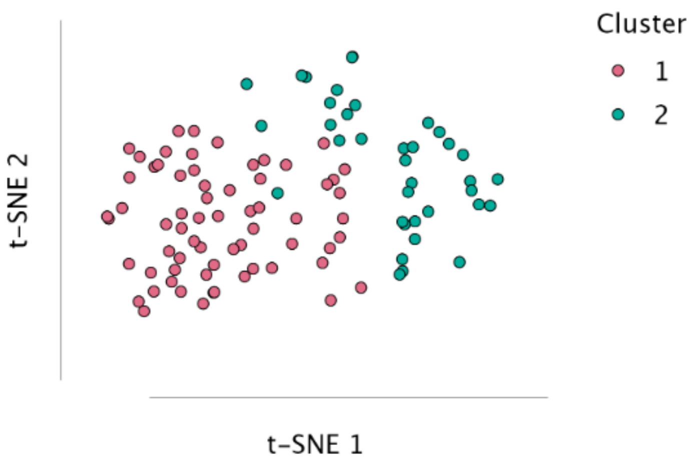


Figure 4.5 t-SNE plot for clusters. Each coloured dot represents one sample in its respective cluster.

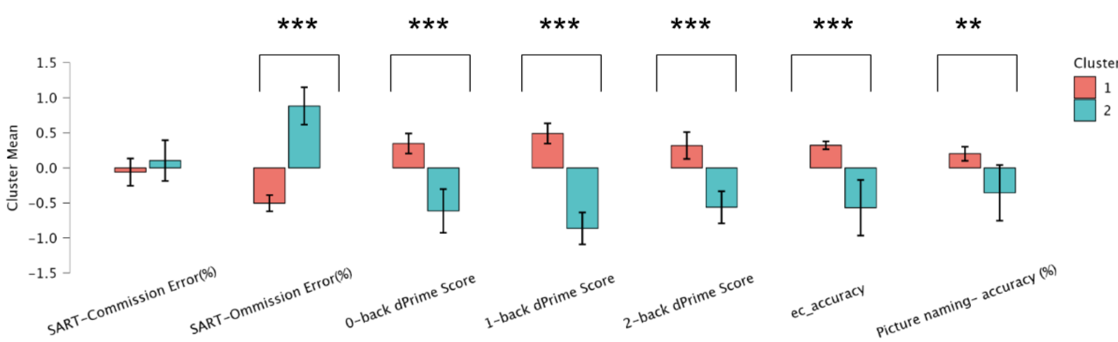


Figure 4.6 Cluster Means for the cognitive scores of the two clusters. Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

Mann Whitney test revealed that Cluster 2 performed poorer than Cluster 1 on all cognitive tasks (Table 4.5). Additionally, SLEDAI-2K scores were significantly higher ($p = 0.017$) for Cluster 2 ($M = 4.7$) than Cluster 1 ($M = 2.3$), along with lower education levels ($p < 0.001$) observed in Cluster 2.

Table 4.5 Cognitive scores [Median (IQR)] for clusters and effect size (Rank Biserial Correlation of Mann-Whitney test) for different cognitive assessments.

Cognitive Tasks	Cluster 1 (n = 65)	Cluster 2 (n = 37)	Effect Size
N-back			
0-back Accuracy (%)	100.0 (2.0)	94.0 (12.0)	0.516***
0-back Hit Rate (%)	100 (6.25)	93.75 (18.75)	0.416***
0-back Miss Rate (%)	0.0 (6.25)	6.25 (18.75)	-0.416***
0-back False Alarms (%)	0.0 (0.0)	2.94 (8.82)	-0.400***
0-back D-Prime	4.65 (0.79)	3.21 (1.62)	0.506***
0-back RT (ms)	680.69 (200.16)	767.39 (211.34)	-0.336**
1-back Accuracy (%)	96.0 (6.0)	84.0 (16.0)	0.739***
1-back Hit Rate (%)	93.75 (12.5)	75.0 (18.75)	0.618***
1-back Miss Rate (%)	6.25 (12.5)	25.0 (18.75)	-0.618***
1-back False Alarms (%)	0.0 (2.94)	11.76 (14.71)	-0.552***
1-back D-Prime	3.48 (0.82)	1.99 (1.28)	0.785***
1-back RT (ms)	704.24 (264.51)	865.93 (248.2)	-0.356**
2-back Accuracy (%)	78.0 (12.0)	68.0 (16.0)	<0.001***
2-back Hit Rate (%)	62.5 (31.25)	50.0 (18.75)	0.488***
2-back Miss Rate (%)	37.5 (31.25)	50.0 (18.75)	0.412***
2-back False Alarms (%)	11.76 (17.65)	17.65 (20.59)	-0.412***
2-back D-Prime	1.51 (1.07)	0.93 (0.91)	0.506***
2-back RT (ms)	864.2 (205.15)	934.18 (237.92)	-0.249*
SART			
Overall Accuracy (%)	87.56 (5.76)	76.0 (9.34)	0.825***
Commission Error (%)	32.0 (28.0)	36.0 (32.0)	-0.079
Omission Error (%)	8.5 (7.0)	21.5 (14.0)	-0.801***
Overall RT (ms)	347.37 (58.46)	358.89 (76.90)	-0.045
ANT			
Executive Functioning Accuracy	0.0 (3.12)	-4.69 (12.5)	0.439***
No Cue RT (ms)	779.47 (190.4)	899.87 (223.83)	-0.395***
Double Cue RT (ms)	768.58 (186.06)	933.24 (199.55)	-0.418***
Central Cue RT (ms)	783.91 (228.0)	869 (212.86)	-0.415***
Spatial Cue RT (ms)	756.19 (186.78)	893.4 (207.64)	-0.400***
Congruent RT (ms)	769.31 (194.37)	895.31 (198.99)	-0.432***
Incongruent RT (ms)	839.61 (246.63)	990.74 (244.38)	-0.415***
Picture Naming			
Accuracy (%)	100.0 (0.0)	100.0 (4.77)	0.259**
RT (ms)	1912.4 (628.9)	2245.5 (637.29)	-0.384**

Note: * denotes $p < 0.05$; ** denotes $p < 0.01$; *** denotes $p < 0.001$

4.5.3.4 Prevalence of Cognitive Decline in Indian SLE Patients

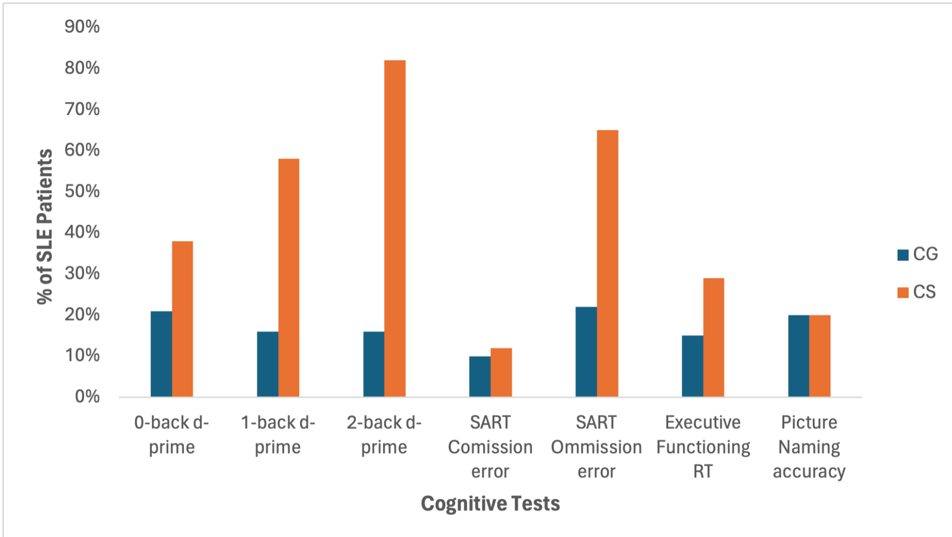


Figure 4.7 Prevalence of cognitive decline in SLE patients compared to the healthy control groups. The percentage of SLE patients with a cognitive decline in each domain is calculated using a threshold of 1.5 SD below the means of the healthy control groups.

We determined the standard deviation (SD) for each patient's cognitive scores by comparing them to the mean and standard deviation of two control groups, CG and CS, as done in a previous study [69]. Our criterion for identifying cognitive decline was set at a threshold of greater than 1.5 standard deviations below the mean of the control groups [121]. Figure 4.7 illustrates the percentage of SLE patients exhibiting cognitive decline in each domain based on this threshold. Compared to CG, 51% of SLE patients displayed cognitive decline (Table 4.6) in at least one of the four cognitive domains evaluated here (working memory, sustained attention, executive functioning and language proficiency). In comparison, when compared to CS, 90% of SLE patients exhibited cognitive decline in at least one of these domains (Table 4.6).

Table 4.6 Percentage of SLE patients with cognitive decline.

	Compared to CG	Compared to CS
>= 1 domain	51%	90%
>= 2 domains	19%	69%
>= 3 domains	1%	32%

4.6 Discussion

The study offers a comprehensive evaluation of cognitive performance among individuals affected by SLE compared to two healthy control groups. We also aimed to capture the heterogeneity of cognitive dysfunction in SLE by exploring the influence of factors such as disease severity and neuropsychiatric manifestations on patients' cognitive health. Furthermore, we identified distinct sub-groups within the patient population through cluster analysis based on cognitive performance and analyzed the factors influencing this variability. Lastly, we determine the prevalence of cognitive dysfunction in our patient population. The following subsections delve into these findings, draw conclusions, and outline future research directions.

4.6.1 Cognitive Functioning among the participant groups

Across various cognitive tasks, SLE patients consistently exhibited poorer performance than college students, while caregivers performed at an intermediate level between SLE patients and college students. Our results indicate that cognitive domains affected in the SLE patient cohort include working memory [122, 123], sustained attention [123, 124], and executive functioning [125], aligning with prior research [122–125]. We also observed poor accuracy in the picture naming task, suggesting deficits in language proficiency [26]. However, no evidence was found for deficits related to alertness and orientation. A significant finding of the study was the notable response latency observed among SLE patients compared to both control groups across all cognitive tasks, suggesting potential impairments in processing speed. Inconsistent findings regarding processing speed impairments have been reported in previous literature [31], with some studies showing no clear difference, while others, like ours, reveal significant distinctions. Research has shown that latencies in linguistic tasks are also affected by attention, inhibition and working memory [126, 127]. We interpret the cognitive task's results in light of their corresponding cognitive functioning and previous research findings focusing on SLE patients.

Research has shown the presence of working memory deficits in SLE patients [122, 123], with some studies also indicating impairments in processing speed [82, 128]. Our results align with the previous studies indicating a correlation between processing speed and working memory demand in SLE patients by highlighting their higher reaction times with increasing load conditions of the N-back working memory task compared to controls [82]. The N-back task imposes cognitive demands related to working memory, attention, inhibition and executive functions, such as cognitive flexibility or updating information [126, 129]. The noticeable decline in task performance among SLE patients with increasing memory load suggests deficits in working memory capacity, cognitive flexibility, and sustained attention, consistent with prior research [82].

Regarding sustained attention, our results align with the studies observing impairments within the SLE patient population [123, 124]. Within the scope of the SART task, the literature suggests a potential trade-off between reaction time and accuracy, where quicker responses are associated with higher error rates [130]. Effective performance on SART task requires executive functions such as response inhibition, vigilance, and alertness [131]. In our study, SLE cases displayed significantly longer reaction times and omission errors, indicating challenges in vigilance and alertness. Surprisingly, they also exhibited the lowest commission errors, suggesting better inhibition. However, statistical analyses did not reveal significant differences between participant groups regarding commission errors, precluding any firm assertions.

Our findings coincide with previous studies that indicate potential executive functioning impairment among SLE patients [125,132], as evidenced by their performance in ANT. SLE cases took significantly longer time to resolve the conflict than control groups while maintaining accuracy. However, alertness and orientation tasks did not reveal any significant difference in the performance. Interestingly, in the SART task, SLE cases showed misses in the alertness task (higher omission errors). The difference between the two results could be due to the nature of the task. ANT demands more spatial attention altertness, whereas SART demands more object based attention altertness. Future studies exploring spatial and object-based attention may help disentangle the conflict in results.

Interestingly, the cognitive tasks utilized in our study engage overlapping brain regions and cognitive functions, highlighting the complexity of cognitive dysfunction associated with SLE. Studies have observed increased blood oxygen level-dependent (BOLD) responses in the prefrontal cortex (PFC) and parietal lobe of SLE patients during working memory tasks compared to healthy controls [133]. Besides working memory, the PFC is implicated in other cognitive functions, including attention and inhibition, suggesting a potential association among these cognitive domains [134, 135]. Moreover, the PFC, inferior parietal lobule, and cingulate gyrus activations are associated with vigilant attention, essential for effective SART performance [136, 137]. Given these findings, further investigation into the cognitive impairments associated with SLE, considering structural brain domains, becomes imperative for a comprehensive understanding of the disease's impact on cognitive function.

Additionally, we evaluated the effectiveness of the Montreal Cognitive Assessment (MoCA) screening task in line with detailed cognitive tasks. Despite the widespread use of the Montreal Cognitive Assessment (MoCA) for cognitive screening, our study uncovered its limitations. Though the average total MoCA score for cases (M = 24.2) was less than the cut-off value (*cut-off score* = 26 [57]), indicating cognitive impairment in SLE patients, it fails to provide a detailed review of it. MoCA primarily focuses on accuracy-based assessments and overlooks response latency, a crucial aspect of cognitive processing. Our study underscores the necessity of employing detailed cognitive tasks to evaluate cognitive function beyond accuracy metrics comprehensively. For instance, while MoCA did not reveal significant differences in memory among our participant groups, the N-back task provided a nuanced assessment of working memory impairment, considering metrics like hit rate, miss rate, false alarms and reaction times. Similarly, although MoCA indicated differences in attention, it lacked specificity regarding which domain of attention was affected. In contrast, our findings revealed that SLE patients exhibited cognitive dysfunction related to sustained attention and executive functioning but not in alertness and orientation. Moreover, while MoCA's picture naming assessment highlighted significantly poorer scores for Cases, it failed to differentiate between accuracy and reaction time. In contrast, our

Picture Naming task unveiled a higher reaction time for Cases than the control groups, indicating slower processing speed. Hence, our results not only align with the findings of this standardised test indicating the presence of cognitive deficits in SLE patients but also provide a comprehensive report of multiple cognitive functions affected in SLE patients.

4.6.2 SLE Disease and Cognitive Functioning

Research has shown conflicting findings regarding the association between disease activity and cognitive dysfunction in SLE patients. While one study indicates an association between disease severity scores (SLEDAI-2K) and cognitive impairment in specific domains like semantic fluency, inhibitory control, and attention [138], others have reported no correlation between disease severity and cognitive performance in SLE patients [139–142]. Our findings add to these observations, as we did not find significant differences in cognitive tasks between SLE patients with varying disease activity levels, except for the N-back task. Interestingly, while there was no significant difference in the lowest load condition (0-back) of the N-back task, a significant difference was observed in the 1-back condition between the two groups. Notably, both patient groups performed equally poorly in the highest load condition (2-back), suggesting the presence of working memory deficits irrespective of disease activity levels. These results underscore the complexity of cognitive impairments in SLE and emphasize the need for further research to understand the underlying mechanisms contributing to these deficits beyond disease severity alone.

The comparison between cognitive performance in Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) and non-NPSLE (NP-) patients has yielded mixed results in previous literature. Some studies report cognitive deficits in both groups without significant differences [143], while others suggest more severe cognitive impairments in NPSLE patients [144]. Additionally, studies have highlighted impairments in short-term visuospatial memory and executive functioning among NPSLE patients [144, 145], while processing speed deficits were not consistently observed [145]. Our study contributes to this discussion by revealing significantly poorer performance of NPSLE patients regarding working memory and attention, consistent with the existing literature [144]. These results collectively suggest that while there may not be a clear-cut distinction in cognitive deficits between NPSLE and non-NPSLE patients in some aspects, there are notable differences in processing speed, attention, and memory functions.

Results from cluster analysis have delineated a clear distinction between the two clusters regarding their cognitive performance across various tasks. These differences were evident in terms of accuracy, error rates and reaction times, with one cluster clearly outperforming the other as previously observed [69]. The underperforming cluster was characterized by higher disease activity and lower education levels. Previous studies [138–142] reveal contrasting findings regarding the association between disease severity and cognitive performance of SLE patients. While our study did not find a significant difference in cognitive performance based on disease severity divisions, the results of cluster analysis hint at a potential link between disease severity and severity of cognitive dysfunction. This underscores the necessity for more specialized investigations to draw definitive conclusions regarding this relationship.

Consistent with previous research, education emerged as a distinguishing factor between the clusters, indicating its potential role in cognitive decline among SLE patients [146]. These findings unveil a layer of heterogeneity in cognitive dysfunction among SLE patients, urging further targeted research efforts to unveil the multifaceted factors contributing to this complexity.

4.6.3 Cognitive Decline in Indian SLE Patients

Our analysis revealed a significant prevalence of cognitive decline among SLE patients, with 51% exhibiting a decline in at least one cognitive domain compared to caregivers. This underscores the notable impact of cognitive decline within the patient cohort compared to a healthy control group matched for age, education, and socio-economic background. Conversely, when contrasted with college students as the baseline, a striking 90% of patients showed signs of cognitive decline in at least one cognitive domain. This variation in prevalence rates emphasizes the influence of diverse demographic factors, such as socio-economic background and education, on comparative studies involving healthy control groups as mentioned in a previous study [69]. In the context of studies investigating the prevalence of cognitive dysfunction in SLE patients, inconsistent findings stem from various factors, including demographics, disease characteristics, study methodologies, and the definition of cognitive dysfunction thresholds [69]. Therefore, establishing standardized thresholds for cognitive impairments that account for these diverse factors across different population groups is imperative.

Despite increasing research attention on the Asian population, there remains a significant gap in well-defined normative baseline data, particularly for the linguistically and culturally diverse Indian population. Future research efforts are crucial for establishing comprehensive baseline data to facilitate more accurate comparisons in this field. Furthermore, while many studies have focused on cognitive screening assessments such as MoCA [147], these assessments provide limited information on specific cognitive domains. Our study represents a pioneering effort in cognitive testing among Indian SLE patients, as we comprehensively assessed multiple cognitive domains using diverse parameters such as accuracy, errors, and reaction times. This approach offers a more detailed understanding of cognitive function in SLE patients beyond traditional screening measures.

4.6.4 Caveats and Future Direction

Our study delves into the cognitive health of Indian SLE patients using a digital neuropsychological battery, revealing significant impairments in processing speed, working memory, sustained attention, language proficiency and executive functioning compared to their healthy counterparts. However, our findings are tempered by the demographic composition of our patient population, primarily comprising females who are homemakers without self-income. This gender skew is not reflected in our control groups, which include both males and females. Therefore, there is a crucial need for future research efforts to collect and analyze data that is gender-balanced to avoid potential gender biases in our results.

Additionally, our study highlights that SLE patients performed poorly compared to college students, who were educationally and economically more privileged. This discrepancy underscores the impact of factors like education and socio-economic background on cognitive functioning, as supported by previous studies linking lower education levels to cognitive decline in SLE patients [146]. Given the low literacy rates in India, particularly among rural populations, it becomes imperative to integrate these socio-demographic factors into future research efforts. Incorporating such factors will enhance the validity and generalizability of cognitive health assessments in diverse populations, ultimately contributing to more effective support for individuals affected by SLE and related cognitive challenges.

Chapter 5

Summary

This thesis significantly contributes to the neuropsychological testing landscape by developing a language-independent digital test battery to assess common psychological and cognitive dysfunctions. We further explore its application in assessing cognitive and psychological health issues associated with a life-altering autoimmune disease, SLE. This chapter presents the key insights of our study in two major sections: firstly, developing a digital neuropsychological battery and, secondly, evaluating its efficacy with Indian SLE patients. Further, we discuss the caveats in our research and propose future directions.

5.1 Development of the Digital Neuropsychological Battery

The developed digital neuropsychological test battery stands out as a pioneering solution addressing critical gaps in the assessment landscape, particularly for low and middle-income countries (LIMICs) like India. The existing English-centric tests require some level of language proficiency and, hence, lack adequate representation of linguistically and culturally diverse populations. Moreover, traditional paper-pencil tests necessitate trained professionals for administration. The skewness of the population in terms of languages, cultures, educational and social backgrounds and the scarcity of trained professionals create barriers to establishing a robust neuropsychological testing platform.

Two primary challenges were tackled through this project. First, we focused on designing tests that transcend linguistic and cultural barriers, ensuring inclusivity across diverse populations varying in languages, cultures, literacy levels, and socioeconomic backgrounds. Second, we aimed to reduce the administrative burden on trained professionals by digitizing the testing process. This transition not only streamlines assessments but also makes way for integrating advanced technologies like functional imaging and eye-tracking in the future. Hence, this work contributes significantly to the field of cognitive and psychological testing in LIMICs, paving the way for more accurate, accessible, and culturally sensitive assessments.

5.2 Psychological and Cognitive Assessment of Indian SLE patients

An integral aspect of this thesis is the application of our developed digital neuropsychological test battery to assess the cognitive and psychological health of Indian Systemic Lupus Erythematosus (SLE) patients. Unlike many studies centered around neuropsychological assessments of SLE patients in Western countries, our research stands out as one of the first studies conducted in India. This emphasis is crucial as it addresses the significant underrepresentation of Indian SLE patients in such studies.

Our data collection efforts included 102 SLE patients and 105 healthy controls, providing a rich dataset for comprehensive analysis. Psychological health results indicated a higher level of anxiety and stress among the SLE patients, along with poor quality of life in physical, psychological, social and environmental domains compared to their healthy counterparts. Our analysis highlighted the intricate nature of mental health challenges among SLE patients, revealing correlations with diverse factors such as social and environmental interactions, physical condition, age, education, and occupation. These complex associations underscore the multifaceted nature of mental health in the context of autoimmune disorders like SLE. This broader perspective contributes to a more holistic understanding of the complex interplay between mental health, disease factors, and socio-environmental influences, emphasizing the necessity for focused research efforts to draw robust conclusions.

Within the cognitive realm, SLE patients exhibited impairments in multiple domains like working memory, processing speed, executive functioning, sustained attention, and language proficiency. Notably, we compared the results of our individual cognitive assessments with the results of the MoCA standardized screening assessment tool. In contrast to our findings in the N-back working memory task, we found no significant difference among the participant groups regarding memory in MoCA. Moreover, MoCA revealed differences in attention but failed to capture the specific components of attention that were affected, as reported in the results of SART and ANT. These findings highlight the limitations of screening tasks in providing detailed information and the need for more comprehensive assessments.

Furthermore, our analysis revealed significant insights into the relationships among disease severity (SLEDAI-2K), neuropsychiatric manifestations (NPSLE and non-NPSLE), and psychological and cognitive functioning in SLE patients. We found no correlation between BILAG scores (reflecting neuropsychiatric manifestations) and psychological health scores, highlighting a crucial gap in existing medical protocols that lack comprehensive information on the frequency, quality, and severity of neuropsychiatric events. Moreover, the associations we observed between SLEDAI-2K scores, neuropsychiatric manifestations, and cognitive functioning underscore the complex nature of cognitive dysfunction in SLE, shedding light on the multitude of factors influencing cognitive functioning. These findings were thoroughly detailed and discussed (Chapter 3 and 4) in the context of existing literature, drawing parallels and distinctions with our results.

While the above-mentioned results highlighted the significantly poorer psychological and cognitive health of the patient population compared to healthy controls, it's crucial to delve deeper into the factors that distinguish individuals within this population. To achieve this, we employed cluster analysis, focusing on the heterogeneity associated with the psychological and cognitive health of SLE patients.

Through this analysis, we divided the patient population into two clusters based on their psychological and cognitive scores separately. This approach allowed us to identify the impact of various factors such as age, education, occupation, and disease severity on the neuropsychological health of patients, moving beyond a simplistic disease-centric perspective. Furthermore, our study contributes to understanding prevalence trends of psychological and cognitive decline within our patient population by comparing them to two distinct healthy control groups. These findings not only highlight the challenges in the diagnosis of cognitive and psychological impairments in SLE patients but also underscore the need for standardized measures for neuropsychological testing in clinical settings.

5.3 Conclusion and Future Direction

In sum, this thesis focuses on designing a prototype by considering several crucial parameters to ensure its effectiveness and relevance to the complex needs of SLE patients within the diverse Indian population. This approach not only acknowledges the unique challenges faced by this population but also aligns with our goal of providing a holistic evaluation framework that captures the multifaceted aspects of health and functioning, such as cognitive health, psychological well-being, and overall quality of life within a limited timeframe. Our work not only fills a critical gap in research but also serves as a catalyst for comprehensive cognitive and psychological testing in India, where awareness and resources for such assessments are often lacking.

Moving forward, there is a pressing need for further standardization and validation of this battery, particularly in young Indian adults. This step is essential to ensure the robustness and reliability of our digital test battery, enabling its extensive utilization in neuropsychological assessments not only for SLE patients but also for individuals with various other medical conditions. Additionally, this will establish a rich normative dataset for healthy controls within linguistically, culturally, educationally, and socio-economically diverse populations. Such a dataset is crucial as a reference point for future studies in the field.

Based on our study results, there is potential for conducting more robust analyses, such as network analysis. We explored the possibility of creating a comprehensive psychological network to uncover correlations between different components of depression and anxiety. Additionally, we sought to examine the association between psychological and cognitive health among participants to unveil the complexities of neuropsychological testing. However, we recognized that such analyses require a larger sample size, possibly twice or thrice the current size. Therefore, while this aspect was scoped out of our project due to sample constraints, it represents a promising avenue for future research and advancements in neuropsychological testing methodologies.

Appendix

Table 5.1 Cognitive scores [Median(IQR)] for Cases, CG and CS for N-back task.

Cognitive Subtask	Cases (102)	CG (52)	CS (53)
0-back Score (%)	98.0(6.0)	100.0(4.0)	100.0(2.0)
0-back Hit Rate (%)	100.0(12.5)	100.0(0.0)	100.0(0.0)
0-back Miss Rate (%)	0.0(12.5)	0.0(0.0)	0.0(0.0)
0-back False Alarm (%)	0.0(2.9)	0.0(3.0)	0.0(2.9)
0-back Total RT (ms)	707.7(208.3)	584.5(282.9)	540.1(156.8)
0-back Hit RT (ms)	707.7(212.6)	580.0(288.3)	544.4(163.1)
0-back dPrime	4.2(1.5)	4.4(0.7)	4.6(0.4)
1-back Score (%)	94.0(12.0)	94.0(8.5)	100.0(4.0)
1-back Hit Rate (%)	87.5(18.7)	93.7(18.7)	100.0(6.2)
1-back Miss Rate (%)	12.5(18.7)	6.2(18.7)	0.0(6.2)
1-back False Alarm (%)	2.9(11.7)	2.9(8.8)	0.0(2.9)
1-back Total RT (ms)	755.9(277.7)	591.7(218.8)	557.6(136.5)
1-back Hit RT (ms)	734.9(278.0)	587.4(228.7)	550.1(150.5)
1-back dPrime	3.1(1.6)	3.4(1.4)	4.6(0.7)
2-back Score (%)	76.0(14.0)	80.0(14.0)	96.0(6.0)
2-back Hit Rate (%)	56.2(35.9)	81.2(25.0)	100.0(12.5)
2-back Miss Rate (%)	43.7(35.9)	18.7(25.0)	0.0(12.5)
2-back False Alarm (%)	13.2(20.5)	17.6(17.5)	2.9(5.8)
2-back Total RT (ms)	884.4(225.3)	834.6(219.2)	728.1(213.6)
2-back Hit RT (ms)	889.2(260.0)	813.5(218.2)	728.1(229.8)
2-back dPrime	1.3(1.0)	1.7(1.0)	3.8(1.5)

Table 5.2 Cognitive scores [Median(IQR)] for Cases, CG and CS for SART, ANT, Picture Naming and MoCA task.

heightCognitive Subtask	Cases (102)	CG (52)	CS (53)
SART			
Overall RT (ms)	351.3(59.4)	324.2(58.1)	291.4(39.4)
GO RT (ms)	380.7(70.3)	347.4(67.7)	314.7(42.5)
NOGO RT (ms)	128.4(121.9)	148.1(140.4)	113.7(64.3)
Overall Accuracy (%)	85.1(11.3)	87.5(9.0)	90.2(3.1)
GO Accuracy (%)	87.7(12.0)	91.5(7.1)	94.5(1.5)
NOGO Accuracy (%)	68.0(28.0)	62.0(32.0)	60.0(20.0)
Commission Error (%)	32.0(28.0)	38.0(32.0)	40.0(20.0)
Omission Error (%)	12.2(12.0)	8.5(7.1)	5.5(1.5)
ANT			
Alerting Score (%)	0.0(4.1)	0.0(4.1)	0.0(0.0)
Alerting RT (ms)	-5.2(41.2)	-8.5(32.2)	-10.8(27.9)
Orienting Score (%)	0.0(4.1)	0.0(2.6)	0.0(2.0)
Orienting RT (ms)	-8.7(53.5)	4.4(37.2)	-7.0(28.5)
Executive Control Score (%)	0.0(3.1)	-1.5(3.1)	-1.5(4.6)
Executive Control RT (ms)	65.1(56.0)	66.9(55.9)	51.2(27.0)
Picture Naming			
Picture Naming Reaction Time (ms)	1997.8(678.5)	1263.4(732.5)	1132.8(347.4)
MOCA			
Total Score	25.0(4.0)	27.0(5.0)	28.0(2.0)

Table 5.3 Psychological Well-being scores [Median(IQR)] for Cases, CG and CS for N-back task.

heightCognitive Subtask	Cases (102)	CG (52)	CS (53)
Psychological Health			
STAI-T	12.0(7.0)	10.0(4.25)	10.0(6.0)
PSS-4	8.0(2.0)	7.0(2.25)	8.0(5.0)
GAD-7	8.0(8.75)	5.0(8.0)	8.0(7.0)
PHQ-9	7.0(7.5)	6.0(7.25)	8.0(6.0)
WHO Quality of Life			
Physical	23.0(6.0)	28.5(6)	29(5)
Psychological	18.0(5.0)	22.0(7.25)	22(6)
Social	10.0(3.0)	11.5(3.25)	11.0(3.0)
Environment	22.0(7.0)	24.0(7.25)	28.0(6)

List of Related Publications

[P1] P Singhal, P Srivastava, L Rajasekhar. **Development of digital neuropsychological battery: A pilot use case in Indian SLE patients**. Oral Papers. Indian Journal of Rheumatology 18(Suppl 2):p S93-S119, — DOI: 10.4103/0973-3698.393682

[P2] P Singhal, P Srivastava. **VARIANT OF NBACK AND SART TASKS - A PILOT VALIDATION STUDY.** Accepted for Poster Presentation at The 10th edition of the Annual Conference of Association for Cognitive Science, hosted at IIT Kanpur from 9th-11th December 2023

[P3] Singhal, P., Srivastava, P., Rajasekhar, L., Samhitha, N. S. (2024). P159 **Development of digital neuropsychological battery: a use case in Indian SLE patients.** Rheumatology, 63(Supplement1), keae163-198, https://doi.org/10.1093/rheumatology/keae163.198

[P4] P Singhal, P Srivastava, L Rajasekhar. **Psychological well-being of SLE patients: A comprehensive examination of stress, depression, anxiety and quality of life.** Submitted to PLOS ONE journal.

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