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(The Role of Cognitive Reserve in Predicting Cognitive Recovery in Right Hemisphere Damage Patients undergoing Neurorehabilitative Treatment)

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Abstract

Background: In the context of cognitive impairments associated with right hemisphere damage (RHD), pragmatic abilities have garnered significant attention as a domain of interest. Pragmatics encompasses the effective use of language in context, crucial for successful communication. Numerous studies have revealed potential deficits in specific aspects of pragmatics, both in production and comprehension, among individuals with RHD. However, a comprehensive understanding of pragmatic abilities in the context of neurorehabilitation remains incomplete, as previous investigations have predominantly focused on isolated facets of pragmatic competence. Specifically, this research investigates the impact of cognitive reserve on the neurorehabilitation outcomes of patients with RHD in relation to their pragmatic abilities.

Methods: Initially, the primary objective is to compare the pragmatic abilities of the Right hemisphere damage participants group with those of the healthy control group using the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS). The RHD patient group comprised 34 individuals, and the control group included 34 healthy participants. Age and education were the key variables employed for matching to rigorously ensure that the demographic characteristics of the control group closely resembled those of the RHD patients. Subsequently, the focus narrows down to a subset of patients who underwent neurorehabilitation, totalling eight individuals. These individuals underwent both pre- and post-treatment assessments using the APACS battery, alongside an evaluation of their cognitive reserve using the Cognitive Reserve Index questionnaire (CRIq). We expanded our analysis by introducing brain lesion percentage and age as independent variables alongside cognitive reserve. This allowed us to investigate their individual and combined effects on pragmatic ability changes, incrementally assessing their contributions to the models.

Results: The statistical analysis revealed a significant difference in APACS Total score and APACS Production score between participants with RHD and the control group, as indicated by independent samples t-test. In APACS comprehension score, the p-value suggests no significant difference between the control and participants with RHD groups, indicating subtle cognitive variations within a shared spectrum. In the subsequent analysis, the investigation highlighted a significant correlation between cognitive reserve and cognitive recovery implying that higher cognitive reserve scores correlated with notable cognitive enhancements post-neurorehabilitation. Subsequently, multiple regression analyses were performed to investigate the factors contributing to these cognitive changes. The change in APACS scores (post-treatment) was regressed against Cognitive Reserve Index (CRI) Total scores. The summary of this analysis demonstrated a significant relationship between cognitive reserve and cognitive recovery. The change in APACS scores was regressed against Brain Lesion Percentage and CRI Total scores. The summary of this analysis revealed the combined effects of brain lesion size and cognitive reserve on cognitive recovery. The change in APACS scores was regressed against Brain Lesion Percentage, CRI Total scores, and age. This analysis explored the additional influence of age on cognitive recovery, alongside brain lesion size and cognitive reserve.

Conclusion: These findings contribute to the existing literature on cognitive reserve and hold implications for clinical practice by emphasizing the advantages of incorporating cognitive reserve considerations into the design of neurorehabilitation interventions.

Keywords: Cognitive reserve, Pragmatic abilities, Right hemisphere damage, Neurorehabilitation, Cognitive recovery

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Chapter 1: Introduction

Neurological disorders encompass a wide range of conditions that affect the central nervous system and significantly impact an individual's cognitive, physical, and psychological functioning. These disorders include but are not limited to stroke, traumatic brain injury (TBI), Parkinson's disease, brain tumors, multiple sclerosis (MS), and various other conditions (Thakur, Albanese, Giannakopoulos, & more, 2016, Chapter 5, p. 87). Stroke occurs when the blood supply to the brain is disrupted, leading to brain damage and often resulting in motor impairments, communication difficulties, and cognitive deficits (National Institute of Neurological Disorders and Stroke, 2023). Traumatic brain injury, caused by a blow or jolt to the head, can lead to a wide array of physical, cognitive, and emotional impairments, depending on the severity and location of the injury Traumatic brain injury, caused by a blow or jolt to the head, can lead to a wide array of physical, cognitive, and emotional impairments, depending on the severity and location of the injury(National Institute of Neurological Disorders and Stroke, 2023). Parkinson's disease is a neurodegenerative disorder characterized by motor symptoms such as tremors, rigidity, and bradykinesia, as well as non-motor symptoms including cognitive decline and mood disturbances (National Institute of Neurological Disorders and Stroke, 2023). Brain tumors, whether benign or malignant, can cause neurological deficits depending on their location and size, leading to a variety of impairments such as seizures, motor dysfunction, and cognitive impairments (National Institute of Neurological Disorders and Stroke, 2023). Multiple sclerosis is a chronic autoimmune disease that affects the central nervous system, leading to a range of symptoms, including fatigue, muscle weakness, balance problems, and cognitive dysfunction (National Institute of Neurological Disorders and Stroke, 2023). These neurological disorders pose significant challenges to individuals and greatly affect their quality of life. Understanding the unique characteristics and manifestations of each disorder is crucial in developing targeted neurorehabilitation approaches to improve functional outcomes and overall well-being for those affected.

RHD, which stands for right hemisphere damage, is another condition that falls under the umbrella of neurological disorders. Like the disorders mentioned earlier, it profoundly impacts various aspects of an individual's life. While conditions like stroke, traumatic brain injury, Parkinson's disease, brain tumors, and multiple sclerosis are well-recognized for their distinct challenges, RHD also presents unique cognitive and communication difficulties. Individuals with RHD often experience disruptions in their pragmatic language abilities, making it challenging to understand and convey nuanced social and communicative cues. Therefore, just as with other neurological disorders, understanding the specific characteristics of RHD is crucial. This knowledge allows for the development of targeted neurorehabilitation strategies that can enhance pragmatic abilities and overall well-being for those affected by this condition. Right-hemisphere-damaged (RHD) individuals have been consistently associated with selective deficits in processing natural language pragmatics, encompassing various aspects such as prosody, nonverbal communication, speech acts, and figurative language (Kasher, Batori, Soroker, Graves, & Zaidel, 1999). These deficits are commonly observed in RHD individuals and can significantly impact their ability to understand and produce language in context. Pragmatic abilities, which encompass the use of language in social and contextual contexts, are particularly affected in individuals with RHD (Kasher et al., 1999). Understanding the nature and extent of pragmatic deficits in this population is of paramount importance as it directly impacts their daily interactions, social relationships, and overall quality of life In Skye McDonald's study, which compared 18 participants with right hemisphere damage (RHD) to 20 matched controls, a comprehensive assessment of pragmatic language abilities was conducted using the Pragmatic Language Battery. Interestingly, the study found that, on the majority of tasks, the RHD participants performed similarly to their non-brain-injured counterparts. The RHD participants demonstrated proficiency in generating indirect nonconventional requests (hints), mirroring the performance of the control group. They also exhibited an equivalent capacity to interpret hints accurately, indicating their competence in understanding indirect communicative cues. Both groups displayed similar performance levels when tasked with interpreting inconsistent (sarcastic) exchanges. However, a significant distinction emerged when assessing the interpretation of literally consistent (sincere) exchanges. The control group consistently performed flawlessly in this regard, while the RHD participants displayed greater variability in their performance. This difference led to a statistically significant disparity, with the RHD group showing a poorer ability to interpret sincere exchanges compared to controls. Additionally, the RHD participants were substantially less likely than the control group to produce requests that effectively addressed the specific concerns of the listener (McDonald, 2000). By the findings from Skye McDonald's study, it is important to note that pragmatic abilities in individuals with right hemisphere damage (RHD) may vary. This means that it cannot be assumed that all RHD individuals will necessarily exhibit impaired pragmatic abilities. To establish the unique pragmatic challenges faced by individuals with RHD, it is crucial to compare their abilities with those of healthy individuals. This control group comparison enables the identification of significant differences between RHD individuals and healthy controls, providing valuable insights into the specific impact of RHD on pragmatic abilities. Understanding the specific nature and extent of pragmatic deficits in RHD individuals is crucial for developing effective rehabilitation strategies and improving communication outcomes in this population.

Within this landscape of neurological challenges, comprehensive neurorehabilitation processes play a crucial role in addressing the multifaceted impact of conditions like RHD, striving to enhance pragmatic abilities and overall functioning in affected individuals. The comprehensive neurorehabilitation process aims to address the diverse challenges posed by neurological disorders, including right hemisphere damage (RHD) and can play a crucial role in improving pragmatic abilities and overall functioning in affected individuals. Neurorehabilitation is the delivery of a coordinated interdisciplinary care program comprising a set of measures that assist individuals who experience disability to achieve and maintain optimal function in interaction with their environment, for maximum independence and social reintegration (Khan, Amatya, Galea, Gonzenbach, & Kesselring, 2016). Neurorehabilitation is a critical and multifaceted process designed to restore or enhance cognitive, physical, and psychological function in individuals affected by a wide range of neurological disorders, including stroke, traumatic brain injury, Parkinson's disease, brain tumors, multiple sclerosis, and other conditions (Khan et al., 2016). These conditions present diverse challenges that impact various aspects of an individual's functioning, such as motor control, sensory perception, cognitive abilities, and emotional well-being. Neurorehabilitation approaches encompass a broad spectrum of interventions, including physical therapy, occupational therapy, speech and language therapy, cognitive training, and psychological support(Khan et al., 2016). By addressing the specific needs and impairments associated with each neurological condition, neurorehabilitation aims to optimize functional recovery, promote independence, and improve the overall quality of life for affected individuals. Understanding the unique complexities of these neurological disorders is essential for tailoring effective neurorehabilitation strategies and achieving positive outcomes.

Furthermore, in this context, the concept of cognitive reserve emerges as a potential influential factor in the outcomes of neurorehabilitation. Cognitive reserve refers to the brain's ability to cope with damage or disease, often resulting in better cognitive outcomes (Stern, 2002). Individuals with higher cognitive reserve may respond more positively to neurorehabilitation interventions, highlighting the importance of considering cognitive reserve when designing and implementing rehabilitation strategies for conditions like RHD (Wilson, 2000).

1.1 Key aspects related to the clinical profile of right hemisphere damage

Right Hemisphere Damage (RHD) is a brain disorder that affects the right hemisphere of the brain and can result from various causes, such as stroke, traumatic brain injury, and tumor resection (Adair & Barrett, 2008). The right hemisphere of the brain plays a distinctive role in various cognitive functions and processes. One of its prominent functions is the specialization in emotional processing and nonverbal functions, encompassing aspects of emotion and perception. While the left hemisphere primarily handles language processing and speech functions, the right hemisphere excels in understanding and expressing emotions, recognizing nonverbal cues like facial expressions and body language, and processing spatial information. This hemisphere's capacity to comprehend emotional nuances and nonverbal communication contributes significantly to our social interactions and emotional experiences. Although there has been popular belief in its exclusive association with creativity, recent research suggests that creative thought engages a widespread network in the brain, rather than relying solely on the right hemisphere. Therefore, the right hemisphere's role extends beyond creativity to encompass a broader spectrum of functions related to emotional understanding, nonverbal communication, and spatial cognition (Corballis, 2014).

Lindell (2006) argues that while the left hemisphere is often considered the dominant language hemisphere, the right hemisphere also plays a crucial role in language processing and production. The right hemisphere is particularly implicated in processing orthography and mediating the prosodic and paralinguistic aspects of language, though it may have lesser ability in processing abstract words and extracting syntax. Lindell also notes that both clinical and imaging research provides evidence for the right hemisphere's linguistic abilities, suggesting that the normal right hemisphere processes language in a distinct fashion and contributes meaningfully to language comprehension. If you are providing a direct quote from Lindell (2006), you should also include the page number of the quote.

According to Barnes (2019), right hemisphere communication disorder is a condition that affects the ability to appropriately relate communicative acts to their context, both in production and comprehension. Individuals with RHD may experience difficulty selecting and efficiently delivering information across multiple discourse types and may have a reduced ability to synthesize different sources of information to reach an appropriate understanding of communicative acts and/

or discourse units. This may result in difficulty with other-initiation of repair, which is used to deal with turns that are likely to receive dispreferred responses or are difficult to integrate with prior talk. Additionally, by producing another other-initiation of repair, a person with RHD may be explicitly signaling a failure to adequately grasp the implications of prior talk, which could be indicative of discourse comprehension deficits. The deficits and symptoms associated with RHD could be reflected in patterns of other-initiation of repair, and there is a need for further empirical studies on everyday conversation and right hemisphere damage. RHD may impact cognitive and pragmatic abilities such as attention, memory, language, and social communication. Furthermore, the right hemisphere's role in processing the paralinguistic aspects of language, such as intonation and tone of voice, highlights its importance in the pragmatic use of language, as these non-lexical features play a crucial role in conveying social meaning and emotions in communication. Gajardo-Vidal et al. (2018) investigated the impact of right hemisphere damage on speech comprehension in stroke individuals and found that such damage can result in long-lasting deficits in speech comprehension that are different from those observed after left hemisphere strokes. Specifically, the study investigated the contribution of the right inferior frontal cortex to linguistic and non-linguistic working memory capacity that is essential for normal speech comprehension. The study used behavioral and lesion data from brain-damaged individuals with functional MRI data from neurologically normal participants. The findings suggest that the right hemisphere is critical for the comprehension of non-literal language and pragmatics, highlighting the significance of these findings for the assessment and treatment of individuals with right hemisphere damage. Clinicians should consider the impact of right hemisphere damage on pragmatic abilities and tailor treatment plans accordingly.

1.2 A Connected Explanation of Cognitive Reserve and Brain Reserve with the CRIq Tool

The cognitive reserve (CR) model suggests that the brain actively attempts to cope with brain damage by using pre-existing cognitive processing approaches or by enlisting compensatory approaches (Stern, 2002, 2009). The concept of cognitive reserve (CR) suggests that individuals with greater CR will be more successful at coping with the same amount of brain damage compared to those with lower CR. This means that the same amount of brain damage or pathology may have different effects on different people, even if factors such as brain size are held constant. This theory proposes that the brain can actively protect itself from damage by utilizing pre-existing cognitive processes or compensatory strategies. The CR model posits that cognitive processes are crucial for explaining the differences between someone who is functionally impaired and someone who is not, despite equal brain changes or pathology. CR is often estimated using proxy variables for lifetime exposures and cognitive activity, such as years of education, measures of crystallized intelligence, and engagement in intellectually stimulating leisure activities. Several studies have shown that higher CR is associated with better cognitive performance and may operate in a compensatory manner even before pathology begins to affect function. Two neural mechanisms have been proposed to explain the role of CR: neural reserve, which refers to the efficiency and flexibility of cognitive networks, and neural compensation, which involves using alternative neural networks to maintain function in the face of pathology (Stern, 2009; Nucci, Mapelli, & Mondini, 2012).

Wilson (2000) explored the multifaceted aspects that play a pivotal role in determining the extent of recovery following brain injury. Numerous factors come into play, including age, severity, and location of damage, cognitive status, and other pertinent variables. Among these factors, age holds significant importance. It has been observed that younger children with focal lesions tend to exhibit more favorable long-term outcomes compared to those with diffuse lesions. Nonetheless, it is crucial to note that age represents just one piece of a complex puzzle that warrants consideration alongside other influential factors (Wilson, 2000).

While brain reserve and cognitive reserve share some similarities, they differ in important ways. Brain reserve is the brain's ability to withstand damage or injury, often due to genetic factors or early life experiences such as childhood brain infections or head traumas. In contrast, cognitive reserve is the brain's ability to compensate for damage or injury by using alternate neural pathways and is influenced by environmental factors such as education, social interaction, and intellectual stimulation (Nucci et al., 2012). Thus, individuals with high levels of brain reserve may be less likely to develop brain injury in the first place, while those with high levels of cognitive reserve may be better equipped to recover from brain injury. Given the potential impact of both brain reserve and cognitive reserve on brain injury outcomes, it is important to compare and contrast these two constructs to better understand their unique contributions to brain injury recovery and rehabilitation.

To standardize the measurement of cognitive reserve (CR), Nucci and colleagues (2012) developed a new questionnaire, the Cognitive Reserve Index questionnaire (CRIq), and a new index, the Cognitive Reserve Index (CRI). The CRIq is designed to measure the amount of CR accumulated by individuals throughout their lifetimes and has potential uses in both experimental research and clinical practice. This questionnaire assesses a range of factors that contribute to cognitive reserve, including educational and occupational attainment, social and leisure activities, and cognitive engagement. The CRIq is a reliable and valid measure of cognitive reserve and has been used in several studies to investigate the relationship between cognitive reserve and outcomes following brain injury (e.g., Marquine et al., 2018; Cicerone et al., 2019). By using tools like the CRIq, researchers can gain a better understanding of how cognitive reserve may impact recovery and outcomes in individuals with brain injuries, and potentially develop interventions to improve outcomes for those with lower levels of reserve.

In their study, Nucci et al. (2012) enrolled 588 participants from the general Italian population, ranging in age from 18 to 102 years old, and divided them into three age groups. Participants were healthy and without any neurological or psychiatric illnesses, and did not receive any compensation for participating in the study. The researchers administered the CRIq in individual sessions lasting about 15 minutes, which included demographic data and 20 items grouped into three sections:

education, working activity, and leisure time. The researchers also administered two tests highly correlated with intelligence: the Vocabulary Test from the WAIS (Italian version) and the Test di Intelligenza Breve (TIB). To quantify the relationship between cognitive reserve and intelligence, the researchers used the raw scores of the three sections of the CRIq and correlated them with age by the number of years an activity had been carried out. The researchers used three linear models to rule out the "age effect." The CRIq subscores were standardized and transposed to a scale with M=100 and SD=15, and CRI (total CRIq score) was the average of the three subscores, also standardized and transposed to a scale with M=100 and SD=15. CRI could be classified into five ordered levels: Low, Medium-low, Medium, Medium-high, and High.

Overall, Nucci et al. 's (2012) study demonstrated the usefulness of the CRIq questionnaire as a measure of cognitive reserve, with potential as a valuable tool in the assessment of cognitive reserve in individuals. Given the potential importance of cognitive reserve in the cognitive recovery of right hemisphere-damaged individuals undergoing neurorehabilitative treatment, the research question for this study is whether cognitive reserve, as measured by CRIq, can explain inter-individual differences in cognitive recovery among RHD individuals. The hypothesis is that a higher level of the cognitive reserve will be associated with a greater improvement in pragmatic abilities, as measured by the difference between pre-and post-treatment scores collected by the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) battery provided by Arcara and Bambini (2016).

1.3 Exploring the Relationship between Cognitive Reserve and Neurological Disorders: Influence on Recovery Outcomes

A review of the literature revealed several studies investigating the association between CR and cognitive outcomes in RHD individuals. These studies utilized various measures of CR, including education, occupational attainment, and leisure activities. Cognitive outcomes were measured using a variety of cognitive tests, such as attention, memory, language, and visuospatial abilities. In addition, some studies investigated the relationship between CR and neuroimaging markers, such as white matter integrity and brain volume.

For example, Rosenich, Hordacre, Paquet, Koblar, and Hillier (2020) have investigated the concept of Cognitive reserve in Stroke Recovery stating that it can reduce the burden of disability resulting from stroke. It is a modifiable factor that can protect against the impact of stroke on cognitive and behavioral abilities. The higher an individual's cognitive reserve, the better the preservation of neural resources and cognitive and behavioral abilities. Engagement in certain activities throughout life can boost cognitive reserve and reduce brain impairment or secondary cognitive impairment as a result of stroke or other neurological diseases. Innovative approaches to increase cognitive reserve and reduce vascular and lifestyle-related risk factors linked to stroke could be the target of self-management programs or novel e-health applications aimed at risk reduction. Physical activity, including aerobic exercise and strength training, has been shown to increase brain volume and preserve cognition, suggesting that brain reserve is more modifiable than previously thought. Future research should explore the benefits of combining aerobic exercise and/or strength training with a cognitive reserve-boosting intervention on outcomes and recovery following stroke. It might demonstrate synergistic or complementary treatment effects above and beyond standalone physical or cognitive interventions (Rosenich et al., 2020).

The article by Campanella, Arcara, Crescentini, Fabbro, and Skrap (2015) provides evidence for the protective effects of cognitive reserve (CR) on language functions in individuals with brain tumors. The study included individuals with brain tumors who underwent language testing, and their cognitive reserve was assessed using a standardized measure. The findings revealed that individuals with brain tumors with high cognitive reserve performed significantly better on language tests compared to those with low cognitive reserve, even when both groups had similar levels of brain damage. Moreover, the study by Campanella et al. (2015) also found that cognitive reserve can protect against the negative effects of brain damage on language functions. Specifically, individuals with brain tumors with high cognitive reserve showed a greater ability to recruit alternative neural networks to compensate for damaged areas in the brain, leading to better language outcomes. These results suggest that cognitive reserve can enhance the brain's ability to adapt to and recover from brain damage, highlighting the importance of preserving cognitive function through activities that promote cognitive reserve. Interestingly, the study by Campanella et al. (2015) also highlights the potential clinical applications of cognitive reserve in the management of brain tumors. In particular, identifying individuals with brain tumors with low cognitive reserve could help clinicians tailor treatments to address potential language impairments and facilitate better outcomes. Additionally, interventions aimed at improving cognitive reserve could help prevent or mitigate the impact of brain damage on language functions in individuals with brain tumors.

Overall, the findings of the study by Campanella et al. (2015) provide important insights into the role of cognitive reserve in language function in individuals with brain tumors. These findings highlight the potential for cognitive reserve to serve as a protective factor against language impairments and the importance of preserving cognitive function in the face of brain damage. Further research is needed to fully understand the mechanisms underlying cognitive reserve and its clinical applications, but the findings to date suggest that promoting cognitive reserve could have significant implications for the management of brain tumors and other neurological conditions.

Despite the growing body of literature on CR and RHD, several discrepancies and limitations exist in the current research. One limitation is the use of heterogeneous measures of CR, making it difficult to compare results across studies. Another limitation is the small sample sizes of many studies, which may limit the generalizability of findings. Furthermore, most studies have utilized cross-sectional designs, which cannot establish causality or determine the direction of the relationship between CR and cognitive outcomes. Despite these limitations, the available research suggests a positive association between CR and cognitive outcomes in RHD individuals. However, further research is needed to determine the underlying mechanisms of this relationship and to establish effective interventions for improving cognitive outcomes in RHD individuals with varying levels of CR.

1.4 The Influence of Cognitive Reserve on Neural Mechanisms and Recovery in Right Hemisphere Damage: Current Models and Moderating Factors.

According to current models of brain plasticity and compensation, cognitive reserve can influence the neural and cognitive mechanisms that support cognitive recovery in individuals with right hemisphere damage (RHD). Cognitive reserve is thought to enhance the brain's capacity for neuroplasticity, functional reorganization, and compensatory strategies, which can help mitigate the effects of RHD (Stern, 2009). Neuroplasticity refers to the brain's ability to reorganize itself in response to injury or environmental demands. Cognitive reserve is thought to enhance neuroplasticity by increasing the brain's capacity to form new connections and adapt to changing conditions. This may be particularly relevant in RHD individuals, as damage to the right hemisphere can disrupt the brain's ability to reorganize and compensate for lost function. Cognitive reserve may help to offset this deficit by providing the brain with additional resources to facilitate neuroplasticity (Stern, 2009).

Functional reorganization refers to the brain's ability to adapt to changes in its environment by reallocating resources to support new functions. The idea that the brain can adapt and reorganize in response to stimulating activities and new learning is supported by the compensatory scaffolding model, which posits that the brain adapts and reorganizes in response to both the neural insults associated with aging and environmental demands. This adaptation and reorganization are thought to be facilitated by cognitive reserve, which increases the brain's capacity to adapt to changing demands. The role of lifestyle factors, such as cognitive stimulation and physical exercise, in promoting cognitive health and offsetting age-related cognitive declines is an area of active research (Goh & Park, 2009).

Compensatory strategies involve using alternative cognitive processes to compensate for deficits in traditional cognitive functions. Cognitive reserve is believed to enhance these compensatory strategies by increasing the brain's capacity to generate new cognitive processes to replace those that are lost or damaged. This is particularly relevant in individuals with Right Hemisphere Damage (RHD), where damage to the right hemisphere can disrupt traditional cognitive processes like attention, perception, and memory. Cognitive reserve may help offset this deficit by providing the brain with additional resources to support compensatory strategies. Several factors can influence the relationship between cognitive reserve and cognitive recovery in individuals with RHD. These factors include age, gender, lesion location, and pre-existing cognitive abilities. The specific location of the brain lesion may determine the extent to which cognitive reserve can assist in particular cognitive functions or brain regions. The study by Chen et al. (2000) indicates that post-stroke motor recovery and functional outcomes are more closely associated with Brain Lesion Profiles (BLPs), which encompass both lesion sizes and primary locations. Notably, these outcomes demonstrated little to no significant correlation with either absolute or relative lesion size alone. This suggests that the combined consideration of lesion sizes and primary locations, as encapsulated by BLPs, plays a more pivotal role in predicting post-stroke motor and functional recovery. Importantly, the influence of delimiting lesion sizes on final outcomes varies significantly depending on the primary lesion locations within the brain (Chen, Tang, Chen, Chung, & Wong, 2000). Importantly, understanding the influence of delimiting lesion sizes on final outcomes, especially when considering the primary lesion locations within the brain, is why we conducted these analyses and controlled for brain lesion size. It allows us to gain deeper insights into how factors such as cognitive reserve and lesion location interact to influence cognitive recovery in individuals with RHD

In conclusion, while the theoretical framework of cognitive reserve has been instrumental in understanding the potential mechanisms underlying neurorehabilitation outcomes in individuals with right hemisphere damage, it is important to recognize its limitations and gaps. Future research should focus on exploring individual differences in the mechanisms underlying cognitive reserve, as well as the potential role of other factors, such as genetics, in its development. By addressing these gaps, a more comprehensive understanding of cognitive reserve and its implications for neurorehabilitation can be achieved. Moving forward, the theoretical framework of cognitive reserve will guide the research design and methodology of this thesis. Specifically, it will inform the selection of appropriate outcome measures, interventions, and statistical analyses. Additionally, the framework will guide the interpretation of the findings and their implications for clinical practice. By utilizing a theoretical framework, this thesis aims to contribute to the existing literature on cognitive reserve and neurorehabilitation, and ultimately improve RHD individuals' outcomes.

The purpose of this study was to examine the relationship between cognitive reserve and cognitive recovery in individuals with right hemisphere damage (RHD) who received neurorehabilitative treatment at San Camillo Hospital Lido di Venezia.

The aim of the study

The primary objective of this study is to investigate the intricate relationship between cognitive reserve and cognitive recovery in individuals with right hemisphere damage (RHD) who are undergoing neurorehabilitative treatment. Specifically, our research aims to achieve the following objectives:

- Evaluating Pragmatic Abilities in RHD Individuals and Healthy Controls: Initially, we seek to ascertain whether discernible differences exist between individuals with RHD and a control group of healthy individuals in terms of their pragmatic abilities, as measured by the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) scores. This comparative analysis will offer insights into the specific impact of RHD on pragmatic skills and the potential efficacy of neurorehabilitation interventions in ameliorating cognitive deficits within this particular population.
- Assessing Cognitive Reserve using the Cognitive Reserve Index questionnaire (CRIq): To gain a comprehensive understanding of the cognitive resources available to RHD individuals,

we will employ the Cognitive Reserve Index questionnaire (CRIq) to quantify their cognitive reserve levels. This instrument is designed to gauge the cognitive reserve that individuals possess, which could play a crucial role in influencing their potential for cognitive recovery.

- Quantifying Cognitive Recovery using APACS Battery: Our study will employ the APACS battery to quantify cognitive recovery in RHD individuals before and after undergoing neurorehabilitation treatment. This battery serves as a robust measure to track improvements in cognitive functioning, particularly in terms of pragmatic abilities.
- Investigating the Relationship Between Cognitive Reserve and Cognitive Recovery: Our central focus lies in exploring whether cognitive reserve levels, as measured by the CRIq, can predict the extent of cognitive recovery in pragmatic abilities following neurorehabilitation in RHD individuals. This investigation will involve analyzing the correlation between CRIq scores and the observed improvement in APACS scores post-treatment. The investigation expands by including both brain lesion percentage and cognitive reserve as predictors to assess their combined impact on language skills. Going further, extending our exploration by incorporating age into the previous analysis. This stepwise approach allowed us to comprehensively explore the unique influences of brain lesion percentage and age and gain insights into their collective contributions to changes in pragmatic abilities.

This research approach employs a step-wise strategy: commencing by validating the pragmatic deficits in RHD individuals through the comparison with healthy controls, then shifting our attention to the crucial relationship between cognitive reserve and cognitive recovery. By addressing these objectives, we aim to shed light on the potential role of cognitive reserve in predicting the outcome of neurorehabilitation interventions for enhancing pragmatic abilities in individuals with RHD.

Chapter 2: Research Methodology

2.1 Participants

Initially, the investigation encompassed two cohorts: individuals with right-hemisphere damage (RHD) and a control group, each comprising 34 individuals. To match the control group with the RHD individuals, a rigorous matching procedure was employed. The control participants were selected from the same geographic region and demographic characteristics as the RHD individuals. Age was closely matched by selecting control individuals within a similar age range as the individuals. This was confirmed by the independent samples t-test for age, which yielded a t-value of 0.46146, degrees of freedom (df) of 61.578, and a p-value of 0.6461, indicating no statistically significant difference in age between the two groups. Furthermore, education level was considered a critical factor, and control participants were selected with educational backgrounds similar to those of the RHD individuals. This was validated by the independent samples t-test for education, which resulted in a t-value of -0.70353, df of 65.008, and a p-value of 0.4842. The analysis revealed no statistically significant difference in education level between the two groups. In both tests, the p-values exceeded the significance level of 0.05, suggesting that there are no statistically significant disparities in age and education between the control and RHD patient groups. The mean age of the control group was 68.35 years (SD = 7.98), ranging from 50 to 87 years, with a mean education level of 10.47 years (SD = 5.10). The RHD individuals group had a mean age of 70.74 years (SD = 9.74), ranging from 45 to 85 years, with a mean education level of 10.26 years (SD = 5.29). The control group represented a reference population without neurological deficits, while the RHD individuals group exhibited various degrees of cognitive and pragmatic impairments.

For the subsequent analysis of cognitive recovery, the study focused specifically on a subgroup of eight individuals with right hemisphere damage (RHD) resulting from either stroke or traumatic brain injury. Among the participants, five were females and three were males, with an average age of 70.375 years, ranging from 45 to 82 (Standard Deviation, SD = 11.93958). Moreover, the participants' educational background, as a significant factor in cognitive reserve, was taken into consideration. The educational distribution of the sample revealed varying levels of education, ranging from 5 to 13 years (M= 8.375 years, SD = 3.1607). These demographic characteristics collectively constitute a diverse and clinically relevant cohort, enabling a comprehensive investigation of the interplay between cognitive reserve and cognitive recovery in RHD individuals undergoing neurorehabilitative treatment. All individuals underwent neurorehabilitative treatment at San Camillo Hospital Lido di Venezia. The treatment program aimed to address the cognitive, physical, and psychological impairments associated with RHD, with a focus on restoring and enhancing the participants' functional abilities. The study obtained ethical approval from the San Camillo Hospital associated with the Bando di Ricerca Finalizzata (protocol number: GR-2018-12366092, Principal Investigator: Giorgio Arcara). All participants provided their informed consent by signing the requisite documentation. The research was carried out at San Camillo Hospital Lido di Venezia, and the data were acquired as part of an ongoing, broader project initiated in 2019, which continues to be active within the Neurophysiology Lab of IRCCS. It is essential to note that individuals who were either unable to provide informed consent due to mental incapacitation or physical limitations were excluded from participation in this study in compliance with ethical guidelines and principles of research integrity.

First and foremost, individuals were required to have experienced a unilateral right hemisphere lesion attributable to a stroke, whether hemorrhagic or ischemic. This criterion ensured that this study focused exclusively on participants who shared a common neurological condition, thus enhancing the internal validity of the research. In addition to the neurological criteria, the absence of other significant pre-existing neurological or psychiatric diseases was a fundamental inclusion criterion. This criterion aimed to isolate the impact of right hemisphere damage (RHD) from confounding factors, ensuring that the observed changes in pragmatic abilities could be attributed primarily to the RHD and its subsequent neurorehabilitation treatment. Furthermore, participants were required to possess the ability to provide informed consent, underlining the ethical considerations and respect for the autonomy of the individuals involved in the study. To determine the eligibility of participants, the Mini-Mental State Examination (MMSE) was used to assess their cognitive functioning. The MMSE is a widely recognized screening tool that evaluates various cognitive domains, including orientation, memory, attention, language, and visuospatial abilities. The "Mini-Mental State" (MMS) is a cognitive mental status examination comprising eleven questions, designed to assess cognitive aspects of mental functions. The administration of the MMSE takes only 5-10 minutes, making it a practical tool for serial and routine use. Unlike comprehensive assessments, the MMSE focuses solely on cognitive functioning, omitting inquiries about mood, abnormal mental experiences, and the form of thinking. Despite its concise nature, the MMSE provides a thorough evaluation of cognitive abilities (Folstein, Folstein, & McHugh, 1975). for more details about MMSE, see Supplementary Materials. The MMSE is scored out of a total of 30 points, and different cut-off values have been established to distinguish between normal cognitive functioning and cognitive impairment in various diagnostic groups. The cut-off value of MMSE<20 on any of the six subtests was chosen in this study to exclude individuals with significant cognitive deficits. The use of the MMSE as a cognitive assessment tool allowed for a standardized and efficient screening process, facilitating the selection of participants who met the cognitive criteria necessary for the study. A table including the details of each patient is reported in the Supplementary Materials.

2.2 Materials

Patients were assessed for pragmatic abilities using Assessment of Pragmatic Abilities and Cognitive Substrates APACS, and Cognitive Reserve using The Cognitive Reserve Index questionnaire (CRIq). The brain lesion size was also assessed using structural magnetic resonance imaging (MRI) measurements.

2.2.1 Cognitive Reserve Assessment

The Cognitive Reserve Index questionnaire (CRIq) was employed as a valuable tool in assessing cognitive reserve in the participants. The CRIq is a reliable and valid tool for assessing CR, which is a critical concept in understanding cognitive outcomes in various neurological disorders. The questionnaire assesses both passive and active cognitive experiences, making it a comprehensive tool for measuring CR. Higher CR scores have been associated with better cognitive outcomes and functional outcomes in various neurological disorders. To administer the CRIq, a semi-structured interview is conducted, and the person administering the questionnaire should have the skills to guide and manage a targeted conversation. It is important to create a respectful and empathetic atmosphere during the interview to encourage the individual to share information effectively.

In a clinical setting, the CRIq should be administered to cognitively healthy individuals. It is important to provide information about the individual's whole adult life, starting from the age of 18 to the present. The questionnaire should indicate whether it was administered directly to the individual or a family member, specifying the identity of the family member in the latter case (for details, see Supplementary Material).

If the person being interviewed has suspected cognitive deficits, particularly in memory or attention, it is preferable to ask the questions to a family member who is well-informed about the individual's past and present habits. The questionnaire is divided into three sections: CRI-Education, CRI-WorkingActivity, and CRI-LeisureTime. The CRI-Education section assesses the individual's level of education. Points are assigned based on the number of school years completed successfully, with 1 point given for each year and 0.5 points for each repeated year. Additionally, training courses lasting at least 6 months are awarded 0.5 points for every 6 months. The CRI-WorkingActivity section focuses on the type and duration of work the individual has engaged in. Different levels of employment are defined based on the cognitive input and level of responsibility required. The years of work in each level are counted, considering only remunerated positions lasting at least one year. Multiple jobs can be counted if carried out simultaneously or in parallel, and the years are rounded up to the nearest 5-year period. The CRI-LeisureTime section examines the cognitively stimulating activities the individual engages in before or after work or school. These activities include a wide range of tasks, such as reading newspapers, domestic chores, driving, leisure activities, using new technologies, social activities, cinema/theater visits, gardening, voluntary work, and more. The frequency and duration of these activities are recorded, and the years of engagement are stated if the activity has been performed often/always for at least 1 year. By gathering information from these three sections, the CRIq aims to assess an individual's cognitive reserve, which can help in understanding their potential resilience to cognitive decline and age-related changes.

One of the strengths of the CRIq is its ability to capture the multidimensional nature of CR, including both passive and active cognitive experiences. Passive experiences, such as education and occupation, provide a foundation for CR, while active experiences, such as engagement in leisure activities, provide ongoing cognitive stimulation that can enhance and maintain CR. The CRIq questionnaire assesses both passive and active experiences, making it a comprehensive tool for measuring CR (Nucci et al., 2012).

Another strength of the CRIq is its ability to predict cognitive outcomes in various neurological disorders. For example, in individuals with Alzheimer's disease, higher CR scores have been associated with better cognitive function, as measured by neuropsychological tests. In stroke individuals, higher CR scores have been associated with better functional outcomes, such as improved activities of daily living and quality of life. Additionally, CR is a potential target for interventions aimed at improving cognitive function in neurological disorders, and the CRIq can be used to identify individuals who may benefit from such interventions.

2.2.2 Neuropsychological assessment of Pragmatic Abilities and brain Lesion Size

The Assessment of Pragmatic Abilities and Cognitive Substrates (APACS, Arcara & Bambini, 2016) test was employed to assess the participants' pragmatic abilities before and after treatment. According to Arcara and Bambini (2016), the APACS test focuses on the assessment of two main pragmatic domains, namely discourse and non-literal language, combining traditional tasks with refined linguistic materials in Italian, in a unified framework inspired by language pragmatics (APACS, Arcara & Bambini, 2016). The test is divided into two main sections, one for production assessment and the other for comprehension assessment, consisting of a total of 6 tasks. The authors derived three composite scores from these tasks (Arcara & Bambini, 2016).

The production score and comprehension score are two important scores derived from the APACS test As illustrated in Figure 1. The production score assesses a patient's ability to produce language that is appropriate in various social contexts, while the comprehension score assesses a patient's ability to understand the meaning of language used in different communicative situations. Both scores are computed based on the patient's performance on the six tasks included in the APACS test. The scoring system used for the APACS test provides a detailed analysis of a patient's performance on each task, allowing for a thorough assessment of their pragmatic abilities.

Interview: This task assesses the ability to engage in conversation through a semi-structured interview. The subject's discourse is evaluated based on parameters of discourse analysis, including speech, informativeness, information flow, and paralinguistic aspects. Grammar and vocabulary errors are also annotated. The frequency of communication difficulties is noted and converted into scores. Maximal score: 44.

Description: This task measures the ability to produce informative descriptions of everyday life situations. The subject is shown ten photographs and asked to describe the main elements depicted in each scene. Scores are assigned based on the identification of salient elements. Maximal score: 48.

Narratives: This task evaluates the comprehension of discourse and narrative texts. Six stories of varying length and complexity are presented, followed by questions. The questions include an open question about the global topic of the story, yes/no questions on specific elements, and questions requiring verbal explanations of non-literal expressions in the story. Scores are assigned based on the accuracy of the answers. Maximal score: 56.

Figurative Language 1: This task evaluates the ability to infer non-literal meanings through multiple-choice questions. Fifteen sentences are presented, including idioms, metaphors, and proverbs. The subject selects the correct figurative interpretation from three options. Each item is scored as 1 or 0 based on accuracy. Maximal score: 15.

Humor: This task assesses the ability to comprehend verbal humor through multiple-choice questions. Seven brief stories are presented, and the subject selects the ending that functions as the punchline. Funny endings play with literal meanings or require deriving unexpected scenarios. Each item is scored as 1 or 0 based on accuracy. Maximal score: 7.

Figurative Language 2: This task evaluates the ability to infer non-literal meanings through verbal explanations. Fifteen sentences, including idioms, metaphors, and proverbs, are presented. The subject describes the meaning of each expression. Responses are scored as 2 for a good description, 1 for an incomplete explanation, and 0 for paraphrasing or providing a literal explanation. Maximal score: 30.

Pragmatic Production composite score: This score is calculated based on the performance in the Interview and Description tasks. The scores from these tasks are transformed into proportions, and the proportions are averaged. Each task contributes equally to the composite score, which ranges from 0 to 1. It reflects the participants' ability to produce pragmatically appropriate discourse.

Pragmatic Comprehension composite score: This score is calculated based on the performance in the Narratives, Figurative Language 1, Humor, and Figurative Language 2 tasks. Similar to the Pragmatic Production score, the scores from these tasks are transformed into proportions and averaged. Again, each task carries equal weight in the composite score, ranging from 0 to 1. It reflects the participants' ability to comprehend pragmatically challenging aspects of language.

Total APACS score: This score is derived as the mean of the Pragmatic Production and Pragmatic Comprehension composite scores. It provides an overall measure of the participants' pragmatic abilities, considering both production and comprehension aspects. The Total APACS score can be used to broadly categorize individuals' pragmatic performance and classify patients based on general notions of pragmatic abilities or for clinical purposes to describe the overall status of pragmatic impairment (for details, see Supplementary Material).

The assessment of brain lesion size constituted a pivotal aspect of this study, a task accomplished through the utilization of structural MRI, specifically employing T1 3D structural MRI scans. Structural MRI excels at rendering highly detailed and precise images of the brain's anatomical structure. In the context of this research, these MRI scans served for data analysis, that is to enable us to quantify the entity of brain lesions in each participating individual. Brain lesion maps were obtained within the team-work, by a standard pipeline. In the first step, lesions were mapped through the ITK-SNAP Software. Then, the percentage of brain tissue normalized to the individual brain volume was obtained and used for the analysis.

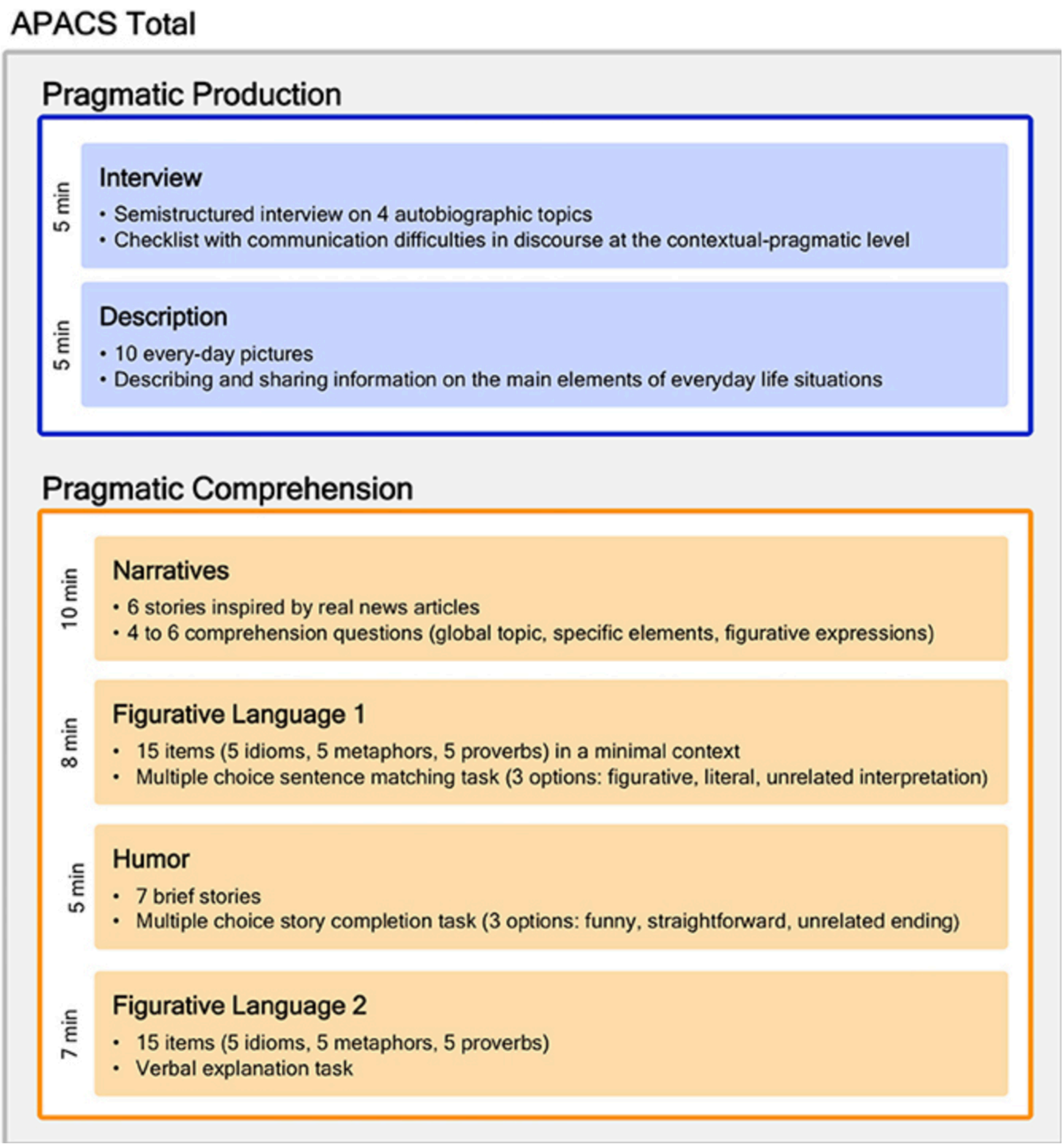

Figure 1:The figure shows the structure of the APACS test. It consists of two sections: Production (in blue), which encompasses two tasks, and Comprehension (in orange), which encompasses four tasks. Adapted from Arcara and Bambini (2016).

Chapter 3: Data Analysis

In our effort to understand how right hemisphere damage (RHD) affects pragmatic abilities, we began with a basic statistical analysis. Initially, we compared individuals with RHD to a group of healthy controls using the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) test. Our specific focus was on assessing the production, comprehension, and total scores of APACS. In our data analysis, we conducted two independent sample t-tests to check if the control group and the RHD individuals group were similar in age and education. This was important to ensure a fair comparison between the two groups.

We conducted Shapiro-Wilk tests for all three APACS scores: production, comprehension, and total, in both the control and RHD participant groups. For the production and total scores, these tests resulted in p-values greater than 0.05, indicating that the data followed a normal distribution. Consequently, we chose to use independent sample t-tests to analyze these normally distributed data. However, when it came to the comprehension score for APACS in the RHD participant group, the Shapiro-Wilk test yielded a p-value below 0.05, suggesting that this data did not follow a normal distribution. To address this non-normality, we opted for the Mann-Whitney U test, a non-parametric alternative to t-tests. This test was appropriate for comparing the two groups in terms of comprehension score, given the non-normal distribution observed in the RHD participant group.

In our analysis of pragmatic abilities, we conducted a paired-sample t-test, comparing mean scores from the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) tool before and after neurorehabilitation treatment. This comparison was performed for a subgroup of eight RHD participants who completed the treatment.

In Model 1 of our analysis, we delved into the possible connection between cognitive reserve and shifts in pragmatic abilities through a multiple regression examination. Our primary emphasis in these regression assessments was on the Cognitive Reserve Index (CRI) total score, employed as the predictor variable. The dependent variable in this case was the difference between the pre- and post-treatment APACS scores. This analytical approach enabled us to investigate whether fluctuations in cognitive reserve notably forecasted alterations in pragmatic abilities within the framework of neurorehabilitation for individuals affected by Right Hemisphere Damage (RHD).

In addition to our initial analysis, Model 1, we conducted further multiple regression analyses, systematically introducing various independent variables to examine their individual and collective influences on cognitive recovery. These subsequent models aimed to provide a more comprehensive understanding of the relationships between cognitive recovery, brain lesion size, age, and cognitive reserve. In Model 2, we expanded our investigation by including both brain lesion percentage and the cognitive reserve as predictors. This allowed us to assess their combined impact on language skills. In Model 3, we further extended our exploration by incorporating age into the previous model (Model 2). This stepwise approach enabled us to comprehensively explore the unique influences of each variable and gain insights into their collective contributions to changes in pragmatic abilities. We introduced each independent variable sequentially into the models to assess how the models' complexity evolved, providing a clearer understanding of their respective impacts on pragmatic abilities.

All statistical analyses were performed using R, version 4.3.1 (R Core Team, 2022), a widely used statistical software package.

Chapter 4: Results

In terms of APACS production, we conducted Shapiro-Wilk tests, which indicated that both the control group (p-value = 0.30) and the RHD participants group (p-value = 0.014) exhibited a normal distribution. However, when we turned to APACS comprehension, the control group's p-value of 0.037 suggested a potential deviation from a normal distribution, while the RHD participants group's p-value of 0.23 indicated a tendency towards conformity with a normal distribution. As for APACS total scores, the results from the Shapiro-Wilk tests showed that both the control group (p-value = 0.12) and the RHD participants group (p-value = 0.39) demonstrated a normal distribution.

Consequently, based on the normality of data distribution, independent sample t-tests are deemed appropriate for APACS production and total scores. However, due to the non-normal distribution observed in the RHD participants group for APACS comprehension, the Mann-Whitney U test is used for comparative analysis in this regard. Regarding the production test, The t-test revealed a statistically significant difference (t = 4.85, df = 40.8, p-value = 1.80) between the means of the control group (mean = 0.92) and the RHD participants group (mean = 0.84). The 95 percent confidence interval ranged from 0.048 to 0.11. Similarly, an independent sample t-test was performed for the APACS total score, which also indicated normal distribution for both groups. The results demonstrated a significant difference (t = 3.26, df = 55.59, p-value = 0.001) in means between the control group (mean = 0.88) and the RHD participants group (mean = 0.82). The 95 percent confidence interval ranged from 0.022 to 0.09.

For APACS comprehension, where the normality assumption was not met for the RHD participants group, the Mann-Whitney U test, a non-parametric alternative, was employed. This test did not provide a significant p-value (p-value = 0.28), suggesting no substantial difference in location shift between the control and RHD participants groups. Table 1 outlines a comprehensive comparison of

APACS composite scores between control participants and RHD participants, highlighting mean values accompanied by their corresponding standard deviations (SD). This comparison offers insights into the variations in pragmatic abilities across the two groups. This finding bolsters the central premise of this study, emphasizing the importance of investigating the impact of right hemisphere damage on pragmatic abilities, and lays a solid foundation for subsequent analytical exploration.

	APACS composite score	
	Mean control (SD)	Mean patients(SD)
Pragmatic Production	0.92 (0.032)	0.84 (0.09)
Pragmatic Comprehension	0.83 (0.09)	0.80 (0.11)
APACS Total	0.88 (0.05)	0.82 (0.08)

Table 1: A detailed comparison of the APACS composite scores between control participants and RHD participants. The table includes mean values along with their respective standard deviations (SD).

To test whether there were differences in pragmatic abilities in RHD participants who underwent cognitive treatment, we conducted a paired-sample t-test using pre- and post-treatment data. Specifically, we compared the mean scores of The Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) tool before and after neurorehabilitative treatment. The results showed a statistically significant difference between the mean scores of the APACS tool before and after treatment ($t=-3.14$, $df=7$, p-value=0.01). The mean difference between the two scores was -0.070, with a 95% confidence interval ranging from -0.122 to -0.017. This suggests that the cognitive treatment resulted in a significant improvement in the pragmatic abilities of the RHD participants. The changes in participants' Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) scores before and after the neurorehabilitation treatment are detailed in Table 2, showcasing the

APACS Production, Comprehension, and Total scores for each individual with right hemisphere damage (RHD), presenting the mean and standard deviation values for APACS Production, Comprehension, and Total scores.

	APACS Production score		APACS Comprehension score		APACS Total score	
	Before Tr.	After Tr.	Before Tr.	After Tr.	Before Tr.	After tr.
Mean (SD)	0.85 (0.07)	0.91(0.05)	0.78(0.12)	0.87(0.07)	0.81(0.07)	0.89(0.04)

Table 2: Displays the mean and standard deviation (SD) of Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) scores before and after treatment. The table provides insights into RHD participants' APACS Production, Comprehension, and Total scores

Figure 2 presents a scatterplot that provides valuable insights into the relationship between cognitive reserve and the changes observed in APACS scores among participants with right hemisphere damage (RHD). Several multiple regression analyses were performed to explore the relationship between cognitive ability changes and different variables.

RHD Participants	Sex	Age	Edu. (Years)	Edu. CRI	WA	Leisure Time	Total CRI	APACS Pro. Before Tre.	APACS Pro. After Tre.	APACS Com. Before Tre.	APACS Com. After Tre.	APACS Total Before Tre.	APACS Total After Tre.
1	F	66	13	108	103	127	117	0.84	0.91	0.83	0.97	0.83	0.94
2	M	82	10	139	119	72	113	0.84	0.85	0.77	0.89	0.81	0.87
3	F	45	8	88	99	92	91	0.93	0.95	0.93	0.91	0.93	0.93
4	M	75	5	96	114	115	110	0.83	0.88	0.75	0.78	0.79	0.83
5	F	79	5	90	71	106	85	0.74	0.88	0.71	0.79	0.73	0.83
6	F	68	8	94	72	144	104	0.92	1	0.93	0.96	0.92	0.98
7	F	80	13	138	127	147	149	0.87	0.94	0.57	0.86	0.72	0.90
8	M	68	5	84	91	82	81	0.98	0.97	0.81	0.81	0.90	0.89

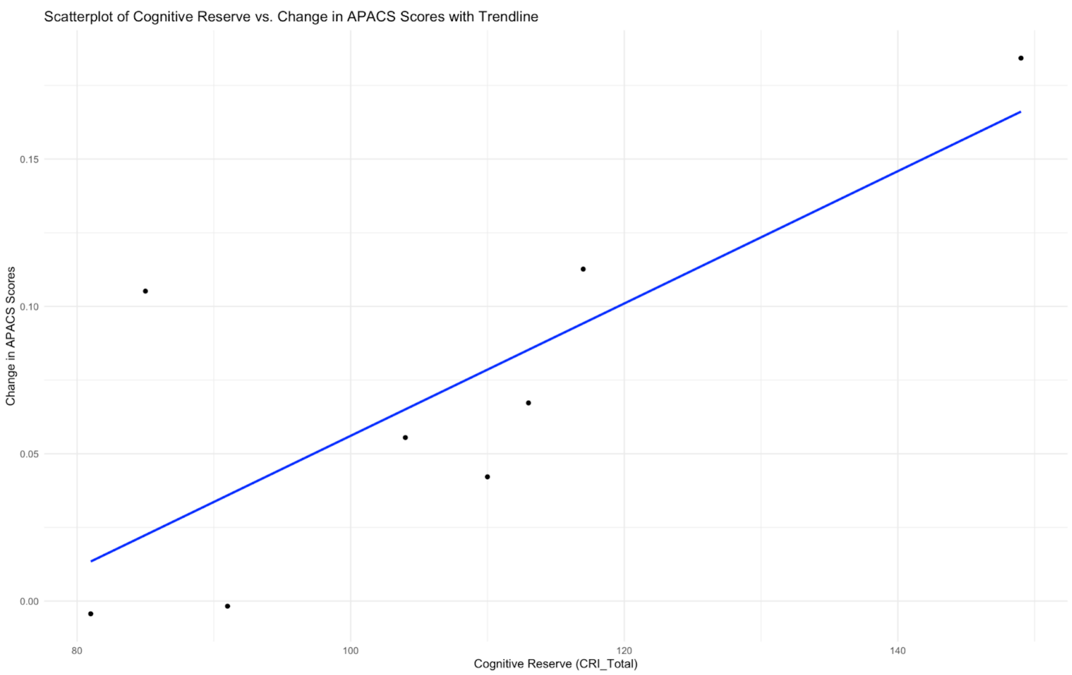

Figure 2: Scatterplot showing the relationship between cognitive reserve and change in APACS scores in RHD participants.

Model 1:The Influence of Cognitive Reserve on Changes in APACS Scores

To investigate the potential relationship between CRI total and the difference between pre-and post-treatment scores in APACS, a multiple regression analysis was conducted. The difference between the score of the APACS total before and after treatment was considered the dependent variable, while the CRI total was used as the predictor variable.

The results of the regression analysis showed that CRI total was a significant predictor of the difference between pre-and post-treatment scores in APACS ($\beta = 0.002$, $t = 3.02$, $p = 0.02$). The intercept was also statistically significant ($\beta = -0.16$, $t = -2.09$, $p = 0.08$). The model had a multiple R-squared value of 0.60, indicating that 60.43% of the variance in the difference scores could be explained by the predictor variable. The adjusted R-squared value was 0.53. The F-statistic was significant ($F(1,6) = 9.16$, $p = 0.023$), indicating that the model was a good fit for the data.

Overall, these results suggest that the CRI total is significantly related to the difference between pre-and post-treatment scores in APACS. Specifically, a higher CRI total score was associated with a great (Model 1). The results from the Cognitive Reserve Index questionnaire (CRIq) are summarized in Table 3, showcasing the scores for CRI Education, CRI WA, CRI LT, and the comprehensive CRI Total score of the 8 participants with right hemisphere damage (RHD).

Table 3: This table provides participant details, including ID, gender, age (years), and education level (years). It also displays Cognitive Reserve Index questionnaire (CRIq) scores for Education, Working Activities (WA), Leisure Time Activities (LT), and the overall CRI Total score. Additionally, it presents Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) scores before and after neurorehabilitation treatment for individuals with right hemisphere damage (RHD). The APACS scores include Production, Comprehension, and Total scores.

Model 2: Combined Effects of Brain Lesion Percentage and Cognitive Reserve on Cognitive Ability Changes

An exploration into the interplay of Brain Lesion Percentage and Cognitive Reserve Index on cognitive ability changes was conducted. The analysis revealed that both Brain Lesion Percentage ($p = 0.03$) and CRIq total score ($p = 0.003$) exhibit significant associations with changes in APACS scores. The initial model disclosed that both brain lesion size ($\beta = 0.007$, $t = 2.89$, $p = 0.03$) and Cognitive Reserve Total score ($\beta = 0.003$, $t = 5.24$, $p = 0.003$) significantly correlated with changes in APACS scores. This suggests that individuals with larger brain lesions and higher cognitive reserve experienced more substantial enhancements in APACS scores post-intervention. The model's adjusted R-squared value stood at 0.79, indicating that 79.32% of the variability in changes in APACS scores can be elucidated by the model's predictors.

This implies that a larger brain lesion percentage corresponds to a more pronounced decline in cognitive abilities. Conversely, individuals with a higher cognitive reserve demonstrate a capacity to mitigate this decline, as evidenced by their less substantial cognitive ability changes.

Model 3: Combined Effect of Brain Lesion Percentage, Cognitive Reserve, and Age on Cognitive Ability Changes

The results of the second model showed that, after controlling for age, cognitive reserve (β=0.003, t=3.73, p=0.02) remained a significant predictor of changes in APACS scores, but brain lesion (β=0.008, t=2.10, p=0.10) and age (β=-0.00, t=-0.27, p=0.79) did not reach statistical significance. This suggests that, while cognitive reserve still significantly predicts changes in APACS scores, the relationship between brain lesion size and changes in APACS scores becomes less clear when accounting for age.

The adjusted R-squared value for this model was 0.74, indicating that 74.62% of the variance in the changes in APACS scores could be explained by the predictors in the model.

Overall, these findings suggest that cognitive reserve is an important predictor of changes in APACS scores following the intervention, even when accounting for potential effects of brain lesion size and age. However, the relationship between brain lesion size and changes in APACS scores may be more complex and warrants further investigation (Models 2 and 3).

			Coefficient (Estimate)					
Model	Intercept Estimate	CRI	Brain lesion size	Age	R-squared	p-value (CRI)	p-value (Brain lesion)	p-value (Age)
Model 1	0.1684-	0.0022	_	_	0.6043	0.0232	_	_
Model 2	0.2410-	0.0028	0.0070	_	0.8523	0.0034	0.0339	_
Model 3	0.2288-	0.0029	0.0077	0.0004-	855	0.0202	0.1033	0.7990

Table 4: Table display regression analyzes results for predicting changes in APACS scores. Model 1 presents estimates, standard errors, t-values, and p-values for 'CRI_Total.' Model 2 provides

coefficients, standard errors, t-values, and p-values, including 'Brain Lesion Size' (in percentage). Model 3 exhibits estimated coefficients, standard errors, t-values, p-values, and asterisks indicating predictor significance, featuring 'Brain Lesion Size' (in percentage).

Chapter 5: Discussion

In our current study, we aimed to explore the pragmatic abilities of individuals with right hemisphere damage (RHD) using a well-established assessment tool known as the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS; Arcara & Bambini, 2016). This tool evaluates pragmatic skills in both the production and comprehension aspects of language. As a preliminary step, we conducted a comprehensive statistical analysis to discern significant differences in pragmatic capabilities between RHD individuals and a carefully matched healthy control group. Our findings unveiled that individuals with right hemisphere damage exhibited notably poorer performance compared to the matched healthy controls, particularly in the domain of Pragmatic Production and the overall APACS Total score. Interestingly, the analysis revealed that RHD individuals performed at a level similar to the control group in terms of Pragmatic Comprehension. This foundational evidence underscores the presence of pragmatic deficits in individuals with RHD and corroborates the anticipated lower APACS scores in this RHD individuals group, particularly in the Total score and production sub-scores. However, notably, no significant differences were observed in the comprehension sub-score.

The absence of significant differences in the comprehension sub-score is a notable finding that beckons further investigation. Several factors may underlie this phenomenon, including the intricate cognitive and neural processes involved in comprehension. Notably, the impact of right hemisphere damage (RHD) on cognitive and pragmatic abilities may exhibit variability contingent upon the location and severity of the brain injury, as evidenced by previous research (Gajardo-Vidal et al., 2018; Lindell, 2006). Our present findings align with prior studies highlighting the multifaceted nature of RHD's influence on language and communication skills. This observation opens up avenues for targeted interventions and rehabilitation strategies, emphasizing the need for future research to unravel the nuances of this intriguing similarity in Pragmatic Comprehension performance between individuals with RHD and the control group.

The results of our study contribute to the growing body of knowledge regarding the intricate relationship between RHD and pragmatic deficits, thereby extending the understanding of how neurological damage can impact language and communication abilities. As the right hemisphere plays a significant role in processing non-lexical features of language and emotional cues (Gajardo-Vidal et al., 2018), the observed pragmatic deficits in RHD individuals underscore the need for tailored interventions and neurorehabilitative strategies that encompass both linguistic and non-linguistic aspects of communication. Ultimately, our research calls for further exploration into the nuances of pragmatic impairments in RHD, contributing to the development of more effective interventions and rehabilitation programs for individuals affected by this condition.

To assess changes in pragmatic abilities following neurorehabilitation in individuals with right hemisphere damage (RHD), we conducted a paired-sample t-test using pre- and post-treatment data from The Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) tool. The analysis revealed a statistically significant improvement in mean scores post-treatment, emphasizing the positive impact of cognitive interventions on RHD individuals' communication skills and overall quality of life. Enhanced pragmatic abilities not only facilitate better social interaction but also contribute to improved social relationships and increased engagement in daily activities. These findings align with the transformative potential of cognitive interventions within the context of RHD neurorehabilitation, as highlighted by previous research (Khan et al., 2016; Tompkins, 2012). Tompkins (2012) emphasizes the multifaceted nature of addressing cognitive-communication disorders in RHD and the need for comprehensive treatment strategies. Our study supports this assertion, demonstrating that effective cognitive interventions can transcend conventional approaches, resulting in significant enhancements in cognitive communication abilities.

Furthermore, our results underscore the principle of functional restoration, a crucial aspect of cognitive rehabilitation (Khan et al., 2016). Effective communication lies at the core of social reintegration and optimal functioning, aligning with the overarching goals of neurorehabilitation

(Khan et al., 2016). Our findings resonate with the concept of neural plasticity, central to neurorehabilitation, as discussed by Khan et al. (2016). The substantial improvements in pragmatic abilities post-treatment underscore the brain's adaptability in response to targeted interventions. This aligns with the broader concept of cognitive recovery suggested by Tompkins (2012), who proposes that cognitive deficits can be addressed through restorative and compensatory strategies, fostering overall cognitive improvement. Importantly, our study's outcomes contribute to the growing body of evidence supporting the effectiveness of cognitive interventions in neurological rehabilitation, echoing the sentiments of both Khan et al. (2016) and Tompkins (2012). Furthermore, the implications extend beyond RHD individuals, aligning with Khan et al.'s (2016) assertion that interdisciplinary neurorehabilitation has the potential to impact a diverse range of conditions affecting communication and cognitive functioning.

To explore the interplay between the Cognitive Reserve Index (CRI) and shifts in APACS scores following treatment, we undertook a comprehensive analysis. This aimed to ascertain if the total CRI score could predict the variance observed in pre- and post-treatment APACS score differences, revealing the potential role of cognitive reserve in the context of neurorehabilitation for individuals with right hemisphere damage (RHD). Through this analysis, we unveil the connection between cognitive reserve and enhancements in pragmatic competencies due to targeted interventions.

Notably, the Cognitive Reserve Index (CRI) total score emerged as a robust predictor of the variance between pre-and post-treatment APACS scores. This underscores cognitive reserve's role in shaping changes observed in pragmatic abilities after targeted neurorehabilitation, even after accounting for other factors.

A higher cognitive reserve score consistently correlated with greater improvements in pragmatic abilities, symbolizing a significant stride towards enriched communication skills and an enhanced quality of life. This observation aligns with the broader principles of neural plasticity and cognitive recovery, affirming the brain's adaptive capacity in addressing deficits and fostering functional gains. Our findings resonate with current models and theories by illuminating the potential mechanisms through which cognitive reserve may facilitate cognitive recovery. As posited by Stern (2009), cognitive reserve appears to foster neuroplasticity, enabling the brain to reorganize and adapt following damage. This aligns with our observation that a higher cognitive reserve index (CRI) total score was linked to notable improvements in pragmatic abilities. Patients with greater cognitive reserve seem to possess enhanced neural adaptability, translating into more substantial gains in post-treatment pragmatic competencies. Furthermore, our study enhances the conceptual understanding of cognitive reserve's role in functional reorganization. The compensatory scaffolding model, as supported by Goh and Park (2009), indicates that cognitive reserve enables the brain to allocate resources effectively to novel functions. Our findings reinforce this notion, suggesting that individuals with higher cognitive reserve are better equipped to reorganize their cognitive processes to compensate for deficits caused by RHD. This adaptive capacity might be particularly valuable for individuals with right hemisphere damage, where conventional cognitive processes are often compromised. Importantly, the integration of cognitive reserve into compensatory strategies offers a compelling explanation for our observed improvements in pragmatic abilities. Our findings echo Stern's (2009) proposition that cognitive reserve enhances the brain's ability to generate alternative cognitive processes, potentially replacing those impaired by RHD. This interpretation is consistent with our data, where individuals with greater cognitive reserve exhibited a greater capacity to leverage compensatory strategies, resulting in more pronounced improvements in communication skills.

In the next step, we hypothesized that higher levels of cognitive reserve would be associated with greater improvement in pragmatic abilities after neurorehabilitation. Our investigation aimed to understand how Brain Lesion Size and Cognitive Reserve Index collectively influence shifts in cognitive abilities. Chen's study (2000) on post-stroke motor recovery and functional outcomes found that Brain Lesion Profiles (BLPs), which encompass both lesion sizes and primary locations, played a dominant role in predicting recovery. These findings align with our analysis, where we examined the impact of Brain Lesion Size and Cognitive Reserve Index on changes in APACS scores. Our results indicated significant associations between both Brain Lesion Size and Cognitive Reserve Index with variations in APACS scores. Specifically, individuals with larger brain lesions and higher cognitive reserves tended to experience more substantial improvements in APACS scores following the intervention. Importantly, the adjusted R-squared value for our model suggests that a significant portion of the variance in changes in APACS scores can be attributed to these predictors. This reinforces the idea that considering both Brain Lesion Size and Cognitive Reserve Index, akin to BLPs, can provide valuable insights into predicting cognitive recovery after neurorehabilitation.

In the outcomes of our last step, after meticulously factoring in age, we observed that cognitive reserve remained a substantial predictor of variations in APACS scores. However, the significance of brain lesion size and age in predicting changes in APACS scores was not evident in this analysis. This implies that, while cognitive reserve continues to hold significance in predicting changes in APACS scores, the association between brain lesion size and these changes becomes less discernible when age is considered.

The current study had several limitations that should be considered when interpreting the findings. Firstly, the relatively small sample size of eight RHD participants limits the generalizability of the results. While the study was able to detect significant differences and relationships within this sample, a larger sample size would enhance the generalizability of the findings and increase the statistical power of the study. Including a greater number of RHD individuals would provide a more representative understanding of the effects of cognitive treatment on pragmatic abilities in the broader population of RHD individuals, reducing the potential for sampling bias and improving the reliability of the results. Future research should prioritize recruiting a larger sample size to overcome this limitation and strengthen the validity and generalizability of the study findings.

Additionally, increasing the sample size would allow for subgroup analyses, such as examining treatment effects based on demographic variables or lesion characteristics, providing further insights into potential moderating factors that may influence treatment outcomes.

Another limitation of the study is the utilization of a single cognitive treatment modality. While the findings demonstrate the effectiveness of the employed treatment, exploring the effects of different cognitive treatment approaches or comparing multiple treatment modalities would provide a more comprehensive understanding of their relative efficacy in improving pragmatic abilities in RHD individuals. Incorporating various treatment approaches would enable researchers to gain insights into specific techniques, strategies, or combinations of interventions that yield the greatest improvements. This knowledge would not only enhance the effectiveness of treatment for RHD individuals but also contribute to the broader field of cognitive rehabilitation. Future research should consider incorporating a range of treatment modalities to uncover the most effective interventions and facilitate the development of tailored and evidence-based treatment protocols.

Additionally, the absence of a long-term follow-up period to assess the durability of the observed improvements in pragmatic abilities is a notable limitation. By solely conducting assessments immediately before and after treatment, the study provides insights into short-term effects but lacks information on the long-term impact of cognitive treatment. To address this limitation, future research should include follow-up assessments at multiple time points, such as three months, six months, and one-year post-treatment. This would allow researchers to track the persistence and sustainability of treatment effects over an extended period. Examining pragmatic abilities over time would provide valuable information regarding the stability and long-lasting benefits of the intervention. Furthermore, a longer follow-up period would allow for the identification of potential factors or circumstances that may influence the maintenance or decline of pragmatic abilities. Future studies should consider incorporating such follow-up assessments to provide a more comprehensive evaluation of the long-term efficacy of cognitive treatment.

Finally, the generalizability of the findings may be limited due to the focus on RHD individuals. While the study provides valuable insights into the effects of cognitive treatment on pragmatic abilities in this specific population, it is important to acknowledge that the results may not fully generalize to individuals with different types of neurological disorders or non-clinical populations. To address this limitation, future research could incorporate a broader range of neurological conditions, such as traumatic brain injury or stroke, and include healthy control groups for comparison. This would allow for a more comprehensive examination of the effects of cognitive treatment on pragmatic abilities across different populations. By including a diverse sample, researchers can explore potential variations in treatment response and identify any condition-specific factors that may influence the outcomes. Furthermore, investigating the efficacy of cognitive treatment in non-clinical populations would provide valuable insights into the generalizability of the intervention beyond clinical settings. Thus, future studies should consider expanding the scope of RHD individuals to enhance the external validity of the findings and ensure the applicability of the results to a broader range of individuals.

Identifying and addressing these avenues for future research is crucial in advancing our understanding of cognitive interventions in RHD individuals and improving overall RHD individual outcomes. Further investigation into these areas will not only enhance our knowledge of cognitive recovery but also contribute to the development of more effective and tailored interventions for individuals with brain injuries.

The study's outcomes hold significant implications for neuropsychology, particularly about cognitive reserve's influence on cognitive recovery in individuals with right hemisphere damage (RHD). The recognition of cognitive reserve's role presents an avenue for tailored intervention strategies, empowering clinicians to optimize rehabilitation programs. These results further bolster the growing body of evidence underlying cognitive reserve's importance in neurorehabilitation, suggesting its potential as a therapeutic focus.

Exploring the link between cognitive reserve and cognitive outcomes offers insights into the intricate interplay of neural plasticity, cognitive processes, and rehabilitation. This understanding could transcend RHD treatment, influencing broader brain injury management. Novel therapeutic approaches targeting specific neural pathways might emerge, facilitating more efficient recovery strategies. In summary, this study's implications span theoretical and practical contexts. It accentuates cognitive reserve's significance in shaping neurorehabilitation interventions for RHD participants while deepening our understanding of neural mechanisms driving cognitive recovery. As a result, the study contributes substantially to advancing neuropsychology, promising enhanced individuals outcomes in both RHD and other brain injury contexts.

Conclusion

In conclusion, our first step involved carefully examining the data to find important differences in how well RHD patients and a matched control group understood and used language in everyday situations. We found that people with RHD struggled more in expressing themselves and in the overall language assessment. However, when it came to understanding language, their performance was similar to the control group. delved into the intricate interplay between cognitive reserve and pragmatic abilities in individuals with RHD undergoing neurorehabilitation. The study contributes to the growing understanding of cognitive reserve and its impact on cognitive recovery, emphasizing the importance of considering individual differences in cognitive reserve in clinical practice. The implications of this research extend to the development of personalized interventions that optimize recovery from pragmatic deficits in RHD patients. Overall, this thesis provides valuable insights into the field of neuropsychology and paves the way for future research on cognitive reserve in the context of neurorehabilitation for RHD and other brain injuries.

Supplementary Materials

The Supplementary Materials for this thesis can be accessed online at:
https://drive.google.com/drive/folders/1Hym4fGEx9sd4uT04cSSUjlR_CLjVAQyt?usp=sharing

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