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Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) for tremor: short and long-term cognitive outcomes

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Abstract

Parkinson's disease (PD) and essential tremor (ET) are two of the most disable conditions among of movement disorders. Traditionally, drug therapy has been the primary method for managing these conditions. However, not all patients respond adequately to initial drug treatments. In recent years, high-intensity focused ultrasound (HIFU) has emerged as a medical procedure for treating various conditions, including tumors, uterine fibroids, and tremors. Magnetic resonance-guided ventral intermediate nucleus (Vim) thalamotomy (MRgFUS-VIM) is as a minimally invasive procedure to the treatment of tipically refractory tremor. By utilizing targeted ultrasound, a lesion is induced in the ventral intermediate nucleus, leading to a reduction in tremors on the contralateral side of the body relative to the targeted nucleus. Nonetheless, despite its minimally invasive nature, the procedure carries risks, such as potential postoperative cerebral edema, leading to complications like speech impairments, gait instability, and weakness in the limbs. Despite the established clinical efficacy, there are current inconsistencies and gaps in the literature concerning potential cognitive deficits post-treatment. Some reports indicate a decline in verbal fluency and verbal memory when targeting the left VIM, while sporadic visuospatial deficits have been noted when targeting the right VIM.

The primary aim of this study was to prospectively assess any short- and long-term cognitive sequeale following the treatment. Following approval by the ethics committee of the University of L'Aquila (08/22), all eligible patients were enrolled in the study and evaluated using a comprehensive battery of neuropsychological, clinical, and behavioral assessments at three distinct intervals: pre-treatment, six months and one year post-treatment. After adjusting for age and education level and confirming data normality via the Shapiro-Wilk test, statistical analyses were performed, employing a paired T-tests or a Wilcoxon signed-rank tests. Significance was determined at a level of 0.003, adjusted using Bonferroni correction for multiple tests (0.05/14). The findings affirm the long-term effectiveness and safety of unilateral MRgFUS treatment, demonstrating sustained cognitive stability over time.

Preface

Parkinson's disease is an idiopathic neurodegenerative condition affecting the central nervous system, characterized by primary motor symptoms like resting tremor, rigidity, and bradykinesia, accompanied by secondary motor and non-motor symptoms. It's a chronic and progressive disease typically diagnosed in the elderly but it can occur across all age groups. Similarly, essential tremor, marked by rhythmic and kinetic tremor during voluntary movements or maintaining posture against gravity, also impacts patients' quality of life negatively. Despite similar motor symptoms, both conditions can involve non-motor symptoms, including cognitive deficits. While drug therapy is the initial treatment for both conditions, not all patients respond adequately to standard drug treatments. For those who don't respond to conventional medical therapies, advanced treatment options such as deep brain stimulation (DBS), levodopa-carbidopa intestinal infusion (LCIG), subcutaneous apomorphine (APOE), and magnetic resonance-guided focused ultrasound (MRgFUS) may be recommended. While the first three therapies are specific to Parkinson's patients, MRgFUS is also applicable to patients with essential tremor refractory to medical therapy. Despite the established efficacy of these treatments, uncertainties or gaps remain regarding potential cognitive deficits post-procedure.

Hence, my doctoral project, under the supervision of Professor Pistoia, aimed to evaluate any long-term cognitive, behavioral, and clinical changes in all eligible patients included in the study undergoing focused ultrasound treatment.

To achieve this, the following studies were conducted:

Study I: **Cognitive outcomes after focused ultrasound thalamotomy for tremor: results from the COGNIFUS (COGNitive In Focused UltraSound) study**. Published in "Parkinsonism & Related Disorders; 2023:106:105230"(first quartile in clinical neurology): this study analyzed cognitive, clinical, and behavioral variables in patients with essential tremor and Parkinson's Disease six months after treatment. Results showed post-operative score improvements at the six-month follow-up in cognitive screening tests (MOCA and MMSE), as well as in quality of life and anxiety-depressive symptoms. Significant improvements were observed when treating the left VIM treatment, while an improvement in quality of life was noted with right VIM treatment. No significant differences in single cognitive domains were found.

Study II: **Cognitive safety of focused ultrasound thalamotomy for tremor: one-year follow-up results of the COGNIFUS (COGNitive in Focused UltraSound) Part 2 study (Published in Front in Neurol. 2024: 17:15:1395282).** One year post-treatment, improvements were found in memory and frontal function domains, along with reduced anxiety and improved quality of life, as measured by the Hamilton-Anxiety Rating Scale, the Quality of Life in Essential Tremor Questionnaire (QUEST), and the Parkinson's Disease Questionnaire-8 (PDQ-8), respectively. Patients with essential tremor showed further improvement in acquisition and consolidation of new information one year after treatment.

In this thesis, an overview will be provided by distinguishing between Parkinson's disease (Chapter 1) and essential tremor (Chapter 2), followed by an explanation of various advanced therapies (Chapter 3). Chapter 4 will present the two major studies conducted during the doctoral program**.** In Appendix A, published studies related to other research projects, educational activities (conference presentations, seminars, training courses), papers under review, and contributions to other research protocols will be listed.

Chapter 1

Essential Tremor

Essential tremor is a motor disorder characterized by involuntary and uncontrollable movements of specific body parts, primarily affecting the upper limbs but potentially extending to other areas including the head, jaw, voice, tongue, and lower limbs. Coined in 1874 by Pietro Burresi, a professor of medicine at the University of Siena, the term "essential tremor" originally described patients presenting with tremor without other overt neurological symptoms. However, recent studies have challenged the notion of essential tremor as solely monosymptomatic, associating it with various additional symptoms and signs such as difficulties with walking, hearing, personality, cognition and mood, highlighting its heterogeneity. Essential tremor is currently the most prevalent movement disorder, typically emerging in adulthood between the ages of 40 and 50, although it can affect individuals of any age. The tremor often manifests symmetrically, affecting both sides of the body, albeit potentially being more pronounced on one side.

While not life-threatening, this disorder significantly impacts quality of life (QoL), hindering everyday tasks like eating, drinking, speaking, writing and handling objects. Additionally, patients with essential tremor may encounter psychosocial challenges such as discomfort, embarrassment and social isolation, heightening the risk of anxiety and depression.

1.2 Etiology and epidemiology of Essential Tremor

Essential tremor, along with other conditions such as Parkinson's disease, exhibits a prolonged asymptomatic or latency period [1-3] This period, combined with the lack of defined biological markers, complicates the identification of risk factors associated with illness. It is essential to understand prevalence and incidence estimates of essential tremor to evaluate its impact on the population and adequately plan healthcare resources. Temporal trends in incidence and variations between different populations can provide crucial indications regarding possible factors of genetic, environmental or biological origin. Studies of the descriptive epidemiology of essential tremor began in the 1960s with a Swedish study conducted by Larsson and Sjögren [4]. However, the diversity of methodological approaches used to identify cases, together with the lack of universally accepted biological markers and diagnostic criteria, has made comparisons between the various studies conducted difficult. In 1997, specific diagnostic criteria for essential tremor were proposed for use in epidemiological and genetic studies [5]. However, there is currently no universal agreement on which criteria to be adopted, and the use of different diagnostic criteria can significantly influence prevalence and incidence estimates. Furthermore, in addition to the variety of diagnostic criteria used, a diversity in the methodology of case identification is observed between the different studies.

Overall, research on the prevalence of essential tremor is limited and shows considerable methodological variability compared to studies conducted on other neurological diseases.

The variation in prevalence estimates across different geographical regions poses challenges in accurately gauging its impact on populations. Broadly, the prevalence of essential tremor is estimated to be 1.13% across all age groups, while among older individuals (aged ≥60 years), it spans from 0.8% to 20.5%. These findings indicate that age serves as a risk factor for essential tremor development, as it for other movement disorders like Parkinson's disease [6]. In individuals aged over 95 years, the prevalence of tremor was calculated to be 21.7 percent [7-15]. Nevertheless, investigations into the prevalence of tremor among children have been constrained by certain limitations. In terms of gender, the majority of studies have reported no notable disparities. However, it's notable that around one-third of population-based studies have reported a higher prevalence among males.[7]

These findings are intriguing, especially considering the potential connection with Parkinson's disease [16-20]. Prior epidemiological studies suggest that a significant proportion of individuals affected by essential tremor remain undiagnosed until identified through population-based studies. As noted, the reasons for this under-diagnosis vary.

Individuals with mild forms of essential tremor often do not seek medical attention, and moreover, tremor is commonly perceived as a normal part of aging, hence not typically assessed for diagnosis or treatment. Overall, the percentage of undiagnosed cases typically surpasses 80%. [7]

1.3 Risk Factors

Although the etiology of essential tremor remains largely unknown, as is the case with many chronic diseases, it is assumed to be the result of a combination of nonmodifiable risk factors, such as aging or genetic factors and modifiable factors, such as exposure to factors that might increase or reduce risk.

1.3.1 Nonmodifiable risk factors

Aging stands out as the primary nonmodifiable factor contributing to the onset of essential tremor. Research across various populations, examining both prevalence and incidence, consistently demonstrates a direct correlation with increasing age. This parallels findings observed in other neurodegenerative conditions, indicating that the cumulative impact of environmental and endogenous factors may interact with an already compromised system due to aging itself [21].

Conversely, family history has been documented in 50% of cases across diverse studies, with prevalence varying from 17% to 100%.

However, the genetics of essential tremor present a multifaceted landscape, with multiple genes influencing disease susceptibility.

In familial cases, an autosomal dominant inheritance pattern is evident, while sporadic forms entail multifactorial inheritance. [22]

Numerous studies have pinpointed genetic susceptibility loci across various chromosomal regions. Additionally, whole-genome association studies have unearthed mutations in genes like LINGO1 and SLC1A2.

Further investigations employing whole-exome sequencing have identified mutations in the FUS/TLS gene, HTRA2, along with variants in the TENM4 gene. [23-30]

In essence, despite the clear genetic component in essential tremor risk, only a handful of genetic variants have been elucidated. This underscores the likelihood that the majority of cases stem from a complex interplay of multifactorial genetic predisposition and environmental influences.

1.3.2 Modifiable Risk Factors

1.3.2.1 Alcohol Consumption

Alcohol is recognized for its ability to alleviate the severity of essential tremor [31,33].

Nonetheless, findings from case-control studies have not definitively established a link between alcohol consumption and essential tremor [34,35].

Alcohol consumption may lead to the loss of Purkinje cells and cerebellar dysfunction, considering the cerebellum's pivotal role in essential tremor's

pathogenesis [36-38]. Hence it is plausible that alcohol intake could impact the likelihood of developing this condition.

1.3.2.2 Caffeine consumption

There has been speculation that consuming caffeine might heighten the risk of essential tremor development due to its adenosine receptor-blocking effect, a neurotransmitter involved in tremor reduction. [39] However, direct correlations between daily caffeine intake and the severity or duration of essential tremor have not been firmly established.

It's worth noting that coffee also contains β-carboline alkaloids, yet no significant associations have been observed between caffeine consumption and essential tremor.

1.3.2.3 Pesticides

Although pesticides have been identified as a risk factor in disorders like Parkinson's disease, the existing evidence doesn't conclusively establish a link between pesticides and essential tremor.

Several studies have indicated no disparities in organochlorine pesticide levels between individuals with essential tremor and those without, nor in their

overall pesticide exposure [35- 40]. However, other studies have suggested a possible correlation between pesticide exposure and essential tremor [41, 42].

1.3.2.4 Exposure to Lead

Two separate studies conducted in New York and Mersin, Turkey, independently found higher lead concentrations in patients with essential tremor. It was hypothesized that the correlation between lead and the risk of developing essential tremor might be linked to the polymorphism of the aminolevulinic acid δ-dehydratase enzyme (ALAD-2 allele) [43].

1.3.2.5 Brain Trauma

There is evidence that head injury may increase the likelihood of developing various neurodegenerative conditions, such as Parkinson's disease[44]. However, there remains insufficient data regarding its association with essential tremor. A study published in 2015 investigated the history of severe traumatic brain injury, characterized by loss of consciousness, hospitalization, or emergency room visits, particularly if occurring at an age of 40 years or older. This study found an elevated risk of developing essential tremor following such trauma [45].

1.4 Factors that May Decrease the Risk of Essential Tremor

1.4.1 Antioxidant-Rich Diet

Numerous studies have explored the impact of various vitamins and antioxidants on the development of neurodegenerative disorders like multiple sclerosis, Lewy dementia, and Alzheimer's disease. However, there is limited information on their role in essential tremor.

For instance, a study involving 156 patients with essential tremor found no significant difference in the consumption of vitamins C and E compared to 220 control subjects [46].

Conversely, another study demonstrated a notable correlation between higher adherence to the antioxidant-rich Mediterranean diet and a reduced risk of developing essential tremor [47].

1.4.2 Smoking Habit

Unlike Parkinson's disease, where several studies have proposed a negative correlation between smoking and the risk of developing the condition, available data for essential tremor are poor.

A study conducted on a Spanish cohort in 2008 revealed that smokers or former smokers had a 50% lower risk of developing essential tremor as compared to nonsmokers [48].

Moreover, a reverse association was observed between the number of pack-years smoked and the risk of developing essential tremor, indicating that

higher tobacco consumption might be linked to a reduced risk of the condition [48].

1.5 Clinical Presentation

From a clinical standpoint, essential tremor primarily presents as postural and kinetic tremors, primarily affecting the distal extremities of the upper limbs, head (with movements of affirmation or negation), and voice.

This tremor may involve both the upper limbs and the head concurrently or may be confined to the upper limbs while potentially impacting any muscle group in the body. Some patients with essential tremor may also experience olfactory dysfunction or neuropsychiatric symptoms such as anxiety, apathy, and depression, similar to individuals with Parkinson's disease.

Unlike parkinsonian tremors, essential tremor reaches its peak amplitude during upper limb movements, coinciding with heightened emotional states. Clinically, there are no discernible signs of persistent muscle weakness (hyposthenia), pronounced paresthesias (except for potential involvement of the median nerve), or alterations in muscle tone (hypotonia and hypertonia).

1.6 Progression of Essential Tremor

The clinical features of essential tremor typically emerge progressively and gradually, affecting both upper limbs bilaterally. Primarily, it presents as a kinetic and postural tremor, characterized by rhythmic oscillations of the involved muscles, typically occurring at a frequency between 8 and 12 Hz. Diagnosis often hinges on the presence of postural or action tremor; however, within essential tremor, the predominant feature tends to be the amplitude of kinetic tremor.

A cross-sectional study involving 369 patients with essential tremor revealed that kinetic tremor was more prominent than postural tremor in 95 percent of cases [49].

Although essential tremor typically affects both sides of the body, it's common to observe mild to moderate asymmetry in the amplitude of tremors. Action tremors, which peak during voluntary movements, vary in severity as the movement progresses and typically occur at frequencies below 13 Hz. Within action tremors, two subtypes are distinguished: kinetic and intentional tremors. Kinetic tremors occur toward the end of a movement, such as reaching a target, and have a small amplitude. In contrast, intentional tremors manifest throughout voluntary movements toward a target, with high amplitude and low frequency. There's often exacerbation upon reaching the target, with a frequency range of 3-10 Hz.

An illustrative example of kinetic tremor is the tremor experienced during the index-nose test, where the patient is instructed to touch the tip of their nose precisely, alternating between both upper limbs, first with eyes open and then closed. Intentional tremor typically doesn't manifest in the early stages of the disease but may have a medium-to-moderate prevalence of 44% in later stages [50].

In contrast to action tremors, postural tremors peak when a limb is maintained in a fixed position against gravity. For instance, patients may be instructed to extend both arms horizontally. To evoke the tremor during this assessment, patients may undergo a simple cognitive task, such as reciting the months of the year in reverse order. Postural tremors typically oscillate at a frequency of 5 to 8 Hz and may vary based on specific postures or tasks, potentially indicating their etiology, as seen in dystonic tremors.

Notably, in postural tremors, the tremor intensity may differ between limbs and decrease when the patient grips objects with both hands [51]. While essential tremor does not pose a threat to life, it significantly impacts one's quality of life and ability to perform daily activities.

1.6.1 Head Tremor

Head tremor typically emerges as a clinical feature evident in the later stages of the disease, with a higher frequency observed among females [52,53].

From a clinical perspective, neck movement during speech has proven to be a valuable indicator for assessing the presence of head tremor. This form of tremor often diminishes when the patient is lying supine, a characteristic that can aid in distinguishing essential tremor from other conditions where head tremor persists even at rest. Individuals with essential tremor may display intentional head tremor. An illustrative instance of intentional head tremor occurs when the head is inclined forward while drinking from a glass [54]. An analysis uncovered that in half of the cases, patients were unaware of the presence of head tremor [55].

1.6.2 Chin or jaw tremor

Chin or jaw tremor is a seldom-seen symptom in essential tremor cases, affecting only 1 to 2 percent of individuals with this condition. Unlike in other disorders where jaw tremor occurs solely at rest, in essential tremor, it usually becomes more noticeable during particular postures or while speaking, displaying characteristics of kinetic tremor [56].

From a clinical perspective, the existence of chin tremor is linked to a more progressed phase of the illness. Patients exhibiting chin tremor are at a higher likelihood of developing hand or voice tremor.

1.6.3 Voice Tremor

Voice tremor is a common clinical feature of essential tremor, often characterized by difficulty maintaining voice volume and increased effort during speech, as indicated by a descriptive study [57].

Many patients may not fully recognize the presence of voice tremor, attributing it to heightened anxiety or emotional states.

Scientific literature suggests that voice tremor typically emerges in the seventh decade following the onset of the condition, with a higher prevalence among females than males. Patients commonly describe their voice as "weak," "unstable," or "hoarse".

Voice, being a multifaceted phenomenon, may reflect dysfunction in specific areas involved in fine movements, such as the tongue and soft palate, despite neurology's traditional focus on language. However, diagnosing voice tremor represents a challenge as it may not always be audible to the human ear, necessitating reliance on the clinician's expertise. To address this, objective rating scales like the Clinical Rating Scale for Tremor (CRST) and Bain and Findley's tremor rating scale have been introduced.

Recent advancements in machine learning algorithms have facilitated the identification of voice tremor in essential tremor patients.

Power spectral analysis has revealed a distinct peak of oscillatory activity within the 2 to 6 Hz frequency range in individuals with evident voice tremor. Leveraging a machine learning vector classifier, voice analysis has demonstrated high accuracy in discriminating between controls and patients with clinically detectable voice tremor, as well as between treated and untreated patients, thereby highlighting the symptomatic effects of medical interventions [58].

1.6.4 Disease Process

Essential tremor is a clinical condition characterized by a progressive course over time, yet only approximately 10 percent of patients who experience it for an extended period develop significant disability [59]. Predictors of disease progression include the duration of the condition, asymmetry of tremors, and the presence of isolated tremors in a single limb [60]. Although rapid disease progression is more frequently observed in older patients, there are similarities noted between the pediatric and adult populations. In pediatric cases, bilateral kinetic tremors of the upper limbs are commonly observed, often accompanied by tremors affecting the voice, head, neck, and legs.

1.6.5 Balance difficulties/gait impairment

Some patients with essential tremor report balance difficulties. Studies have tested balance by assessing tandem gait and using posturography [60-63]. Patients with essential tremor perform worse than age matched controls in balance testing.

1.6.6 Alcohol responsiveness

Approximately 50% of individuals with essential tremor experience symptom relief when consuming alcohol. This responsiveness to alcohol is not exclusive to essential tremor and tends to be more frequently reported by patients with earlier onset of symptoms. However, there aren't specific historical features that reliably predict whether a patient will respond to alcohol. Despite concerns about a potential increase in alcoholism among those with essential tremor, research studies have not substantiated this claim. [64-66] A study testing alcohol responsiveness demonstrated a peak effect approximately 45 minutes after consumption in a sample of 10 patients, with sustained benefit observed within the initial 90 minutes.[67]

1.6.7 Psychiatric Symptoms

Numerous studies investigated the personality traits and psychiatric conditions associated with essential tremor.

It has been observed that depression and anxiety levels are notably elevated among individuals with essential tremor when compared to those without the condition, resembling patterns often found in Parkinson's disease [68-70].

Anxiety, sometimes experienced as an internal tremor, is a common phenomenon among patients.

Moreover, findings from a cross-sectional case-control study indicate that essential tremor patients not only exhibit higher rates of depression and anxiety but also suffer from increased sleep disturbances and fatigue compared to their healthy counterparts. Furthermore, this study revealed that individuals with essential tremor reported more severe pain, as assessed by the Brief Pain Inventory-Severity, along with greater interference from pain, as measured by the Brief Pain Inventory-Interference, compared to controls. [71]

1.6.8 Cognitive symptoms

The recent evolution of cognitive decline in Essential Tremor (ET) traces back to thorough psychometric evaluations conducted prior to thalamic deep brain stimulation (DBS) for ET patients resistant to medication.

The implanted brain hardware held the potential to modulate neurological functions with minimal morbidity.

The initial exploration into ET neuropsychology was published in 1999, involving a comparison of 40 patients who underwent comprehensive psychometric assessments before and three months after DBS [72].

Subsequent findings revealed potential associations between frontal lobe impairments, cerebellar dysfunction, and cognitive decline. [73-74] In essence, recent years have seen the documentation of various cognitive abnormalities in both clinical and population-based studies of ET patients.

There has been a paradigm shift from viewing Essential Tremor solely as a disorder with one symptom to recognizing it as part of a spectrum encompassing other neurological manifestations, such as mild cognitive decline and dementia.

There exists a consensus that cognitive deficits in ET patients are mild. These abnormalities affect approximately 30-60% of individuals with ET.

The primary cognitive deficits observed includes:

- **Deficits of attention–concentration and working memory.**

In people with essential tremor (ET), numerous studies have shown deficits in attention and concentration. These deficits have been assessed using various cognitive tests, with results indicating significant alterations in several areas.

- **Cognitive Tests Used and Results:**

Wechsler Adult Intelligence Scale (WAIS) - Digit Span (forward and backward)

Test that measures the ability to memorize and repeat sequences of numbers.

Results: Several studies have found impaired performance in patients with ET. [74-75]

Brief Test of Attention (auditory):

Test that measures the Assesses auditory attention.

Results: Alterations observed in many patient series. [73]

Stroop Test (auditory and visual attention):

Test that measures the ability to ignore irrelevant information and maintain attention on specific tasks.

Results: Abserved poor in several series. [73-75]

Wisconsin Card Sorting Test (WCST):

Test that measures complex attention and other related psychological functions.

Results: Alterations found in various studies. [73-76]

Wechsler Memory Scale (WMS) - Visual Span (forward and backward):

- Measures visual working memory.
- Results: Deficits detected in some studies. [74]

Symbol Search and Trail Making Test (TMT) [77-80]:

- Symbol Search: Assesses processing speed and visual search.

TMT Series A: Measures attention and completion time.

TMT Series B: Assesses executive functions.

Results: Disturbances observed, except in the study by Sahin et al. [76]

- **Deficits in executive functions**

Executive functions, which include the overall and sequential control of multiple cognitive operations, are thought to be dependent on the frontal lobe, particularly the dorsolateral prefrontal cortex (DLPFC), or their connections with the thalamic-cerebellar axis. These functions can be assessed through motor tests, such as the go-no-go paradigm, fist-edge-palm test, Luria loop test and others, and through psychometric tests. [76,79]

- **Assessment of Executive Functions:**

- **Motor Tests**:

  Motor tests, which mainly assess motor control and inhibition, do not show significant differences in patients with essential tremor (ET). This is because such tests are generally positive only in patients with severe frontal deficits.

- **Psychometric Tests:**

  "Frontal" psychometric tests assess a wider range of psychological functions, including:

- Complex Attention

- Planning

- Flexibility and Mental Control

- Verbal Fluency

- Social Behavior

- Intuition

- **Examples of Psychometric Tests**

  WCST (Wisconsin Card Sorting Test): Assesses cognitive flexibility.

  Stroop Test: Measures attention and inhibition skills.

Trail Making Test (TMT) Part B: Examines attention and ability to switch between different tasks.

Results of Tests in Patients with ET

Verbal Fluency: Tests such as Letter-cued Word Fluency (FAS) and the Letter-cued Word semantic test are affected, indicating a dependence on DLPFC. [73,74 -78,79]

Front Assessment Battery (FAB): Specific to detect frontal deficits, showed statistically significant alterations in recent studies. [80]

Matrix Reasoning (WAIS): Slightly abnormal in one study. [75]

Tower of London and Tower of Hanoi: Require executive and visuospatial skills, results in normal range in ET patients. [73-74]

Clock Drawing: This test, which assesses executive and visuospatial skills, also showed normal results in patients with ET. [73]

Conclusion

Psychometric tests provide a more detailed assessment of executive functions than motor tests. In patients with essential tremor, many of these executive functions may be impaired, although motor tests do not show significant differences unless there are severe frontal deficits.

- **Deficit in Explicit Memory**

  Different types of memory, such as working, short-term and delayed memory (verbal learning), but not implicit memory (unconscious memory of acts), have been assessed in patients with essential tremor (ET). [81]

- **Assessment of Memory in Patients with ET**

  Verbal Memory Test:

  California Verbal Learning Test (CVLT) [77]:

  This is the most frequently used measure. It is found to be impaired in almost all clinical series, although with variations in the different subscales.

  Hopkins Verbal Learning Test (HVLT) [79]:

  Used in a study that demonstrated significant reductions in memory in patients with ET compared to controls.

  Wechsler Memory Scale (WMS-R) [75]:

  The full scale or its subscales have been used in several clinical series with variable results. The logical memory subscale was abnormal in one series but not in others, such as that of Tröster et al. where only 12-15% of ET patients

were 1 SD below the normative group. The figural subscale showed influences in another series.

Visual Memory Test:

Rey-Osterreith Complex Figure Test (ROF) [76,79]:

It showed no statistically significant differences from controls in two studies. In Kim et al.'s investigation, only the recognition subscale of the ROF showed a statistical deficit. Other visual tests, such as the face test (WMS) and the visual reproduction subscale (WMS), showed impairments in some studies.

Conclusion

Only verbal memory (recognition, immediate and delayed) was found to be consistently impaired in ET patients, while visual memory is probably impaired to varying degrees. Tests such as the CVLT and HVLT showed memory problems in ET patients, while the results of the Wechsler Memory Scale were more variable.

- **Deficit in language** [74-75]

As noted, several verbal fluency tests showed consistently lower results in ET patients. In addition, other language tests such as the Benton Naming Test (BNT) were also affected, although with more variable results.

Verbal Fluency Test:

Letter-cued Word Fluency (FAS) and similar tests:

These tests have consistently shown lower performance in patients with ET than in controls.

They indicate difficulty in generating words based on specific letters or categories, reflecting potential deficits in executive functions related to verbal production.

Benton Naming Test (BNT):

This test assesses the ability to correctly name objects depicted in pictures.

Results in patients with ET have been more variable:

Some studies have found that patients with ET perform lower than controls. [74-75,79]

Others, have reported less consistent results, with some series of patients showing no significant differences from controls. [76]

Conclusion

In patients with ET, verbal fluency tests consistently show lower performance than controls, indicating specific difficulties in executive and language functions.

The Benton Naming Test (BNT) showed more variable results, suggesting that the impact on language may be less consistent and may depend on specific factors not yet fully understood.

1.6.9 Neuropsychological comparison between PD and ET

ET and PD show similar deficits in specific aspects of neuropsychological functioning, particularly those related to the integrity of the prefrontal cortex, suggesting involvement of frontocerebellar circuits [80]. These circuits are characterized by lower performance in functions such as attention, executive function, memory and naming. Comparing patients with PD and ET, lower performance was observed in tests of verbal fluency, digit span, visuospatial tasks, memory, attention, and abstraction processes. [73-74]. These results suggest a similar cognitive profile for the PD and ET groups in the absence of dementia and an overlap in the cognitive domains involved. Studies highlight that the clinical picture of ET and PD goes beyond motor features, showing cognitive effects even at an early stage. In PD, cognitive features are attributed to dysfunction of the basal ganglia circuit. Similarly, there is strong evidence suggesting dysfunction of the cerebellum-thalamus-cortical circuit in ET. The

thalamus is highly implicated in the modulation of cognitive performance and is a key subcortical relay for the prefrontal cortex. Connections with the frontal lobes could be impaired in both diseases, thus explaining the similar cognitive profile.

1.6.10 Diagnosis

The current diagnostic approach to essential tremor relies primarily on a thorough clinical assessment. During this evaluation, clinicians meticulously examine the distinctive signs and symptoms of essential tremor, while also gathering pertinent patient history, including family medical background. Various tests are conducted during the neurological examination, encompassing evaluations such as arm extension, nose index, spiral drawing, and other specialized procedures. These examinations reveal tremor variations across different contexts. A comprehensive neurological assessment is crucial for precise diagnosis, as essential tremor can mimic other conditions like Parkinson's disease or dystonic tremor. Comparative research involving patients with essential tremor and those with Parkinson's disease has unveiled disparities in tremor presentation during arm extension, notably with essential tremor often exhibiting more pronounced tremor near the wrist than in finger movements [81-82]. For accurate diagnosis within a clinical setting, a commonly employed tool is the CRST scale (Figure1). This scale is specifically crafted to gauge both the qualitative and quantitative aspects of tremor

amplitude, divided into three distinct sections. Part A enables the evaluation of tremor amplitude across various body regions, including the head, face, voice, and tongue, while also delineating the amplitude of resting, postural, and kinetic-intentional tremor, specifying the limb involved (right or left) and its segments (upper or lower).

Part B facilitates the assessment of tremor amplitude during the execution of fine motor tasks, employing the spiral test. Finally, Part C facilitates the evaluation of tremor severity during daily activities, assigning scores on a Likert scale ranging from 0 to 4 within each subscale.

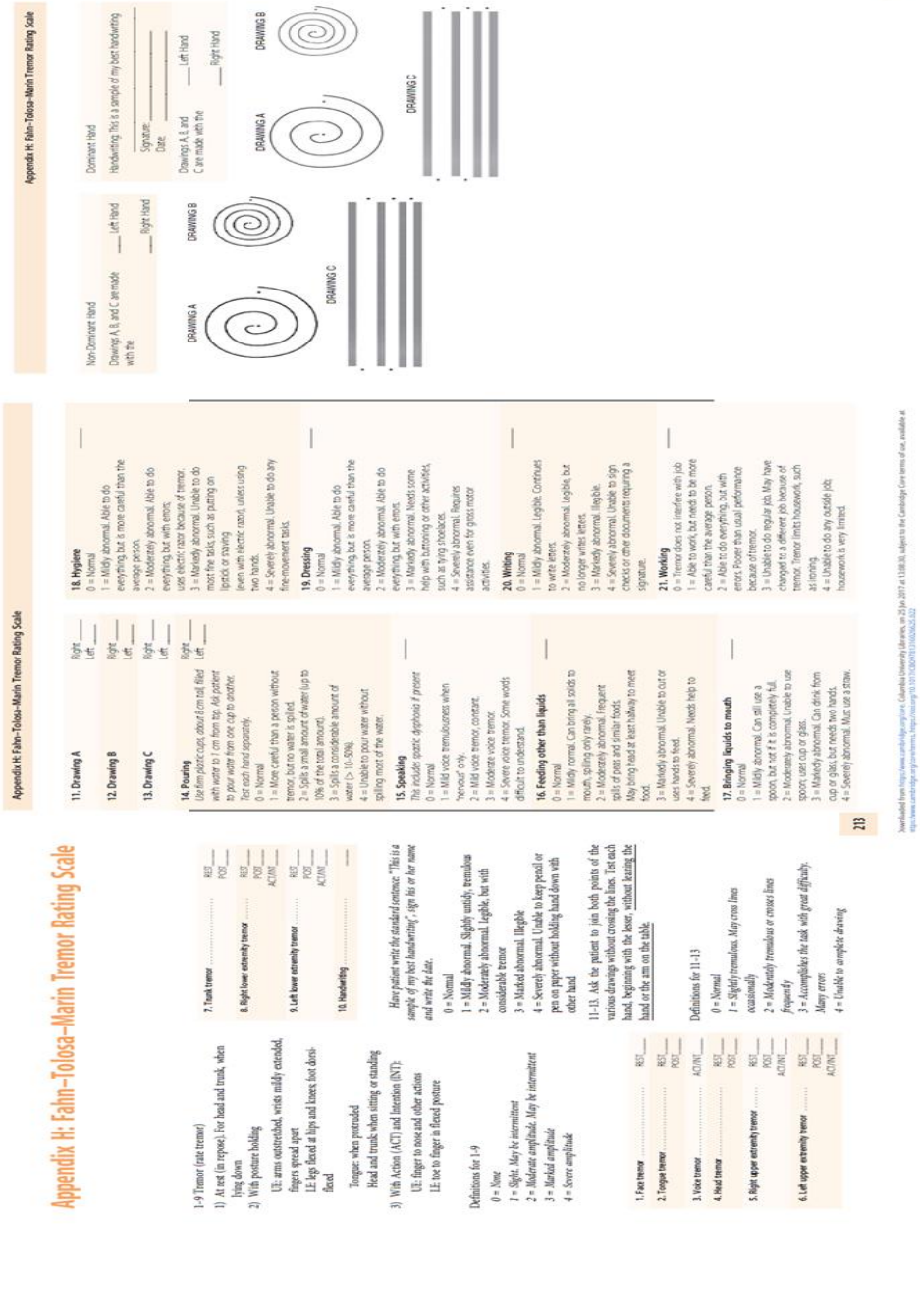

Figure 1 Clinical Rating Scale for Tremor (CRST)

1.7 Classification of essential tremor

The classification system aims to recognize the range of symptoms associated with essential tremor, which primarily manifest as action tremor in the arms. The updated criteria delineate essential tremor as a distinct tremor syndrome characterized by exclusively action tremor persisting for a minimum of three years.

However, the presence of tremor in other regions such as the legs, head, or voice is permissible. Tremor is categorized as isolated postural or kinetic if it has been present for less than three years. Importantly, the absence of other neurological conditions like dystonia, ataxia, or parkinsonism is required for essential tremor diagnosis. A related condition termed "essential tremor plus" retains the essential tremor criteria while permitting the presence of additional neurological signs like dystonia or cognitive impairment. Exclusion criteria for both essential tremor and essential tremor plus encompass isolated focal tremors in the head or voice, orthostatic tremor exceeding 12 Hz, task-specific or position-specific tremors, and an abrupt onset of symptoms followed by gradual deterioration.

However, the consensus statement does not precisely delineate the scope and features of these additional "soft" neurological signs, resulting in new uncertainties and queries. For example, a patient developing a rest tremor is classified as having essential tremor plus, even though this tremor could indicate a parkinsonian sign or the progression of essential tremor.

1.8 Treatment

The treatment of symptoms associated with essential tremor is recommended for individuals whose daily activities are significantly impacted by the tremor.

In the 1970s and 1980s, certain medications were identified as first-line treatments for symptom management, although their effectiveness was observed in only a limited number of patients over the short term.

However, the long-term efficacy of these medications remained uncertain. Presently, recognizing essential tremor as a multifactorial syndrome, it is acknowledged that the response to pharmacological therapy may vary among patients. Both the American Academy of Neurology and the Italian Movement Disorder Association have outlined specific medications that can be considered as first, second, or third-line options for tremor management. Table 1 shows the main recommended drugs. [83-85]

Drugs	AAN guidelines	IMDA guidelines
Propranolol, propranolol LA: nonselective β adrenergic receptor antagonist	First line therapy	First line therpy
Primidone: metabolized to phenylethylmalonamide and phenobarbital; effect is independent of its phenobarbital metabolite	First line therapy	First line therpy
Topiramate: stimulation of GABA activity; inhibition of carbonic anhydrase; antagonizes AMPA/ kainite receptors; blockade of voltage dependent calcium and sodium channels	Second line therapy	First line therpy
Gabapentin: interacts with auxiliary subunit of voltage sensitive calcium channels102	Second line therapy	Second line therapy
Alprazolam: positive allosteric modulators on GABA-A receptor	Second line therapy	Second line therapy
Clonazepam: positive allosteric modulators on GABA-A receptor	Second line therapy	Not recommended
Zonisamide: inhibits T type calcium channels; weak inhibitor of carbonic anhydrase	Not recommended	Second line therapy
Olanzapine: DA receptor blocker	Not recommended	Second line therapy
Clozapine: DA receptor blocker	Third line therapy	Second line therapy
Nimodipine: calcium channel blocker	Third line therapy	Not recommended

Table 1 Drugs recommended for the treatment of Essential Tremor

Chapter 2

Parkinson's Disease

Parkinson's disease and atypical degenerative parkinsonisms (Parkinson Plus) are part of the spectrum of extrapyramidal system disorders. Clinically, they manifest with motor function impairments ranging from decreased movement (bradykinesia/kinesia) and increased muscle tone (rigidity) to the emergence of abnormal involuntary movements (hyperkinesias) [86]. Parkinson's disease, an idiopathic central nervous system disorder, presents with primary motor symptoms such as tremor, rigidity, and bradykinesia, along with secondary motor symptoms and various associated non-motor symptoms.

This chronic, progressive neurodegenerative disorder predominantly affects the elderly but can occur at any age. Initially described by Parkinson in 1817 as "shaking palsy" to highlight its main motor symptoms (bradykinesia, rigidity, and tremor), its clinical features were later delineated by Charcot in 1872. The neuropathological identity of the disease was established by Trietiakoff in 1919, emphasizing consistent alterations in substantia nigra [89]. Typically, onset occurs around 65-70 years of age, with a slightly higher prevalence in men than in women (M: F=3:2).

Recent decades have seen a rise in the disease's incidence and prevalence, partly attributable to population aging [87].

However, improved diagnostic accuracy and environmental factors like prolonged survival and exposure to toxins such as pesticides or chemicals may also contribute. Various epidemiological studies have reported Parkinson's disease prevalence estimates ranging from 1 to 2 per 1000 in unselected populations, affecting 1 percent of individuals over 60 years old. It's rare before age 50, accounting for less than 5% of cases in population-based cohorts before age 40 and peaking at 4% in older age groups. Early-onset cases are often associated with genetic variants, though monogenic forms are rare in unselected populations but may be prevalent in certain ethnic groups. Genetic factors are implicated in 5-10% of cases, possibly more.

Incidence rates vary widely across studies due to methodological disparities, with annual rates ranging from under 10 to over 20 per 100,000 population. However, incidence studies may underestimate diagnoses, especially among older individuals [88].

Parkinson's disease imposes significant disability on patients, leading to progressively worsening impairments over time, and burdens caregivers, negatively impacting quality of life and mortality rates.

2.1 Risk Factors

The cause of Parkinson's disease remains elusive, yet it is widely acknowledged that a combination of factors contributes to its onset and progression, encompassing both genetic and non-genetic elements.

The involvement of genetic factors in Parkinson's disease is evident from the increased susceptibility observed in individuals with a family history of the condition or related tremors.

This is further supported by the existence of monogenic forms of Parkinson's disease, characterized by Mendelian inheritance patterns (either dominant or recessive). The pioneering gene identified in this context is SNCA, which encodes the α-synuclein protein, leading to a severe and early-onset manifestation of the disease through autosomal dominant transmission with notable penetrance. Subsequent discoveries have revealed other genes such as LRRK2 and PRKN (encoding parkin), associated with early onset, a high incidence of dystonia, and autosomal recessive transmission. In idiopathic cases, the primary genetic risk factor arises from mutations in the GBA gene, responsible for encoding the β-glucocerebrosidase enzyme deficient in Gaucher disease.

This mutation, found to be five times more prevalent in Parkinson's patients than in healthy individuals, is linked with an earlier onset, increased prevalence of cognitive impairment, and REM sleep behavior disorder (RBD) compared to typical Parkinson's disease cases in non-carriers. Advancements in genomic research have led to the identification of additional genetic risk factors, particularly involving single nucleotide polymorphisms at various loci, including GBA as well as genes associated with monogenic forms of Parkinson's disease (such as LRRK2 and SNCA). [89,90]

Although the majority of Parkinson's disease cases are sporadic, with genetic influences accounting for only a fraction of the overall risk, considerable attention is directed towards investigating non-genetic factors contributing to disease onset. Within this contexct, constitutional factors such as sex, ethnicity, and age play significant roles as established risk determinants. Notably, Parkinson's disease exhibits a male predominance, with a male-to-female ratio of approximately 3:2. Studies conducted in the United States indicate the highest incidence among individuals of Hispanic ethnicity, followed by non-Hispanic whites, Asians, and blacks. Age also emerges as a pivotal risk factor, with the prevalence and incidence of Parkinson's disease increasing nearly exponentially with advancing age, peaking notably after the age of 80.

2.1.1 Lifestyle and enviromental Factors

Several studies have explored the relationship between lifestyle habits and the onset of Parkinson's disease (PD). Certain habits have been identified as protective factors against PD, while others are associated with an increased risk. Physical activity, smoking, coffee consumption, and moderate alcohol intake have all been found to have a protective effect, significantly reducing the risk of PD. [91]

Conversely, dietary habits also play a role, with specific factors linked to a higher risk of developing the disease.

Increased consumption of milk, carbohydrates, and overall calorie intake has been associated with a greater risk of PD. On the other hand, a higher intake of dietary fats has been shown to significantly decrease the risk of PD.

The risk of developing Parkinson's disease is also influenced by various environmental factors. Exposure to pesticides, herbicides, insecticides, and solvents, as well as paraquat, hydrocarbons, living in rural areas, are all factors associated with an increased risk of the disease.

Conversely, there is evidence suggesting that exposure to sunlight for at least 15 minutes per week is negatively correlated with the development of PD [92,93].

2.2 Comorbidities and medical history

Exploratory studies have investigated the connections between Parkinson's disease development, medical history, and concurrent health conditions. Findings indicate that depressive disorder, bipolar disorder, and constipation are positively linked with the onset of the disease, with their presence exacerbating the risk. Two hypotheses have been proposed to explain these associations: some research suggests these factors may act as prodromal symptoms, while others argue they represent independent risk factors [94,95].

Additionally, a familial history of Parkinson's disease or tremor is a significant risk factor. Furthermore, diabetes and a history of head injury also notably elevate the risk of Parkinson's disease.

2.3 Medications

Certain medications have been identified as potentially protective against Parkinson's disease development, including ibuprofen, calcium channel blockers, and thiazolinediones (TZDs). Conversely, beta-blockers and aspirin have been associated with an increased risk. It is imperative to identify non-genetic, modifiable factors and accurately assess their predictive value in order to prevent Parkinson's disease development and modify its natural progression.

This is crucial given that clinical diagnosis typically follows a prodromal phase that may span several years or even decades. Nongenetic factors can trigger Parkinson's disease pathogenesis and influence its progression during this phase [96].

2.4 Etiopathogenesis

The disease is characterized by the targeted depletion and loss of specific neuron populations, primarily affecting dopaminergic neurons in the pars compacta of the substantia nigra, truncal aminergic neurons in the locus coeruleus, cholinergic neurons in the nucleus basalis of Meynart, and cortical neurons.

As per Braak's hypothesis, the progression of Parkinson's disease involves typical neurodegeneration, initially impacting regions such as the medulla oblongata (specifically, the dorsal motor nucleus of the vagus) and the olfactory bulb (Braak's stages I and II).

This degeneration then extends to encompass areas including the substantia nigra and locus coeruleus, deeper mesocortical structures, the hippocampus, and limbic structures (Braak stages III and IV), eventually affecting associative neocortical and primary regions (Braak stages V and VI).

Neuropathologically, a series of molecular alterations occur:

- α-synuclein misfolding and aggregation lead to the formation of Lewy bodies and Lewy neurites in surviving neurons and proximal axons, respectively.
- Mitochondrial dysfunction is observed.
- Impaired protein clearance, involving the ubiquitin-proteasome and autophagy-lysosomal systems, results in inadequate elimination of degraded proteins and an increase in autophagic vacuoles. Autophagy-related proteins are found within Lewy bodies.
- Evidence of neuroinflammation and oxidative stress is seen through abnormal immune responses, elevated proinflammatory cytokines, changes in immune cell populations, aberrant microglial activation, and features of neuroinflammation in experimental models.
- Deficiencies in neurotrophic factors, excitotoxicity, and dysregulation of the iron metabolic pathway are implicated in neuronal death, with increased iron levels leading to heightened free radical production.
- Aggregation of α-synuclein by iron, defects in mitochondrial complex I, and the neuroprotective effects of iron chelators contribute to neuronal death through apoptosis or necrosis.

These mechanisms collectively contribute to a prolonged process of neuronal degeneration, influenced by various stressors. Identifying a singular primary

cause is challenging, as these pathophysiological processes likely intersect, initiating a cascade of insults that ultimately result in irreversible cellular damage [97].

Histologically, Parkinson's disease primarily manifests significant alterations in the midbrain region. These alterations encompass widespread pallor of the substantia nigra, resulting from neuronal loss, accompanied by reactive microglial gliosis and the presence of free melanic pigment. A hallmark histological change in Parkinson's disease is the presence of Lewy bodies, which may have implications for disease progression. Lewy bodies are composed of polymers of α-synuclein and appear as round hyaline cytoplasmic inclusions with a clear peripheral halo and an acidophilic central part.

Although the Lewy body has conventionally been regarded as the primary histological feature, its precise role in the disease process remains uncertain. Additionally, reactive microgliosis is observed, which in Parkinson's disease transitions from a protective to a pathological state. This transition is characterized by alterations in cytokine levels, including elevated TNF-α and increased i-NOS. Glial cell activation may contribute both to dopaminergic cell death and as a response to neuronal loss.

The primary alterations in neuronal transmission observed in Parkinson's disease include:

- Dopaminergic deficiency, stemming from the degeneration of dopamine-producing neurons due to the aggregation of protein clusters. This deficiency constitutes the focal point of primary treatments for Parkinson's disease, which aim to restore dopamine levels.
- Hyperactivity within the basal nuclei.
- Disturbances in serotonin and norepinephrine levels in the striatum and alterations in the GABAergic system within the substantia nigra. The GABAergic system deficiency is typified by a deficit in glutamic acid decarboxylase, leading to disrupted functioning of the stylo-nigral GABAergic projections responsible for regulatory inhibition.
- These alterations contribute to certain symptoms of Parkinson's disease being resistant to traditional dopamine therapies [98].

  There is a close relationship between the extent of neuronal loss, the degree of dopaminergic depletion, and the severity of clinical symptoms. The preclinical phase of Parkinson's disease involves progressive neuronal loss and dopamine depletion in the striatum, accompanied by reductions in homovanillic acid, tyrosine hydroxylase, and DOPA decarboxylase, along with compensatory hypersensitivity of dopamine receptors.

2.5 Clinical Presentation

Parkinson's disease is characterized by four primary clinical features: Resting Tremor, Rigidity, Akinesia (or bradykinesia) and Postural instability (which typically emerges later in the disease progression).

Additionally, characteristic symptoms include camptocormia (a forced posture in flexion) and motor blocks.

Tremor is the initial motor symptom in 60% of cases, and in the early stages, motor symptoms often manifest unilaterally or asymmetrically. [99]

Beyond these motor symptoms, Parkinson's disease presents with a broad range of non-motor symptoms affecting various systems and organs, most commonly involving the gastrointestinal, genitourinary, and nervous systems, often accompanied by psychiatric manifestations. These non-specific symptoms may go unnoticed or unreported by patients due to embarrassment or lack of awareness of their correlation with Parkinson's disease. However, it is crucial to recognize them as they can serve as prodromal symptoms occurring up to ten years before the onset of characteristic motor symptoms. [100]

The disease progression is nonlinear, with greater advancement typically observed in the early stages and in patients with prominent postural instability. Non-motor symptoms also play a significant role in the disease course.

It is essential to evaluate the disability caused by both motor and non-motor symptoms on an individual basis, considering the diverse profiles and lifestyles of individuals with Parkinson's disease and addressing the unique needs and goals of each patient. [101]

2.5.1 Motor Symptoms

Bradykinesia, a key feature of Parkinson's disease, refers to a generalized slowing of voluntary movements. While it is a hallmark clinical sign of Parkinson's, it can also be present in other conditions like depression. In contrast, akinesia indicates a reduction in both voluntary and involuntary movement, affecting automatic, reflexive, and associated actions.

Bradykinesia arises from dysfunction in the basal nuclei, resulting in deficiencies in the facilitation of the supplementary motor area by the thalamo-cortical pathway and inappropriate activation of primary motor regions.

This impairment leads to difficulties in movement planning, initiation, execution, as well as in performing sequential and simultaneous tasks. [102]

Typically, the initial manifestation of bradykinesia is a delay in executing daily activities and a prolongation of reaction times. Tasks requiring fine motor skills, such as buttoning clothing or handling tools, may become notably challenging.

A characteristic feature of bradykinesia is the reduction of spontaneous movements, including facial expressions and mimicry, resulting in hypo-amimia.

Patients may display a lack of emotional expression, with fixed facial features, reduced blinking, and a slightly open mouth, giving rise to a vacant stare. Furthermore, impairment in associated and automatic movements, which typically occur without conscious effort, such as gestures during conversations, is observed.

Bradykinesia is often the initial neurological symptom in individuals with Parkinson's disease. Its severity may fluctuate depending on the patient's emotional state; for example, individuals who are particularly stimulated by a situation may demonstrate brief bursts of rapid movement, known as "paradoxical kinesia." This phenomenon suggests that Parkinson's patients retain intact motor programs but struggle to access them without external sensory cues. [103]

2.5.1.1 Rigidity

Rigidity is a prevalent symptom in about 89% of individuals diagnosed with Parkinson's disease. It presents as heightened muscle tone, which patients perceive as stiffness, and examiners observe as sustained resistance to passive movements with equal intensity in opposing muscle groups.

This resistance is often described as "plastic" or "lead-like" and is periodically interrupted by rhythmic interruptions known as the "cogwheel" phenomenon. Rigidity typically affects all muscle groups, initially impacting axial and proximal musculature like the neck, shoulders and hips before extending to limb musculature such as the wrists and ankles. [104]

In cases where rigidity significantly affects flexor and adductor muscles, it can result in a camptocormic posture. The precise pathophysiological mechanisms underlying rigidity remain largely unclear. However, previous neurophysiological observations have suggested alterations in excitability within cortical and subcortical pathways. These changes are evidenced by abnormalities in long-latency stretch reflexes and the co-activation of agonist-antagonist muscles during passive movements. Such alterations likely lead to increased reactivity and endurance of muscle spindles. Additionally, degeneration of nuclei in the brainstem, particularly the locus coeruleus, raphe nuclei, and the pontomedullary reticulospinal system, may contribute to changes in noradrenergic and serotonergic influences on spinal motor control pathways through descending pathways.

Consequently, changes in excitability within spinal interneurons and motor neurons, triggered by sensory inputs, may contribute to the manifestation of muscle stiffness. [105]

Various factors can influence rigidity, with cold temperatures, emotional states, and fatigue exacerbating symptoms, while relaxation typically occurs during sleep.

2.5.1.2 Tremor

Tremor, particularly at rest, often serves as the initial and most prevalent symptom in Parkinson's disease. Initially appearing on one side of the body and typically localized to a finger or thumb, it may progress to involve an entire limb or both limbs as the disease advances. Rest tremor in Parkinson's disease typically exhibits a lower frequency (4-6 Hz) compared to essential tremor and becomes most pronounced when the limb is at rest.

This tremor diminishes or disappears altogether during voluntary movement and is absent during sleep. It commonly affects the distal segments of the upper limbs, characterized by a distinctive "counting coins" motion involving the adduction-abduction movement of the thumb and flexion-extension of other fingers. Involvement of the lower limbs, chin, jaw, and tongue is less frequent and may occur in advanced stages. Notably, tremor can persist for several years without other accompanying parkinsonian symptoms.

In addition to rest tremor, many Parkinson's patients experience postural tremor, also known as "reemergent tremor," which may be more pronounced and disabling than rest tremor and has a higher frequency (6-7 to 9-11 Hz).

Postural tremor manifests as a brief pause of tremor upon assuming a postural position [108].

The pathophysiological mechanisms underlying tremor in Parkinson's disease are still under debate.

While the severity of tremor does not directly correlate with dopamine deficiency in the substantia nigra, it appears to be associated with degeneration of the retrorubral area, another dopaminergic nucleus projecting to the globus pallidus internus. Furthermore, neurotransmitters such as acetylcholine and serotonin may play a role, with some patients responding better to serotonergic medications than dopaminergic ones [106].

The noradrenergic system has also been implicated in tremor, with studies suggesting less degeneration of the locus coeruleus (the primary source of brain noradrenaline) in tremor-related Parkinson's disease and increased noradrenergic receptor binding in the locus coeruleus. Situations that activate the noradrenergic system, such as cognitive and physical stress, can exacerbate tremor [107].

Cerebellar involvement in tremor pathogenesis is also suggested, with evidence of cerebellar gray matter loss in specific regions in patients with resting tremor.

Recent research proposes involvement of two circuits in tremor pathogenesis: the basal ganglia and the cerebello-thalamo-cortical circuit.

2.5.1.3 Postural instability and deformities

Postural instability often becomes pronounced in the later stages of Parkinson's disease, coinciding with the decline in postural reflexes, rendering the patient unable to effectively correct imbalance. This symptom typically emerges after other Parkinsonian symptoms have already manifested.

Postural instability primarily manifests as anteropulsion, significantly increasing the risk of falls. Assessment of balance commonly involves the pull test, although its utility in gauging stability in daily life situations is limited. During the pull test, the patient is pushed backward or forward from the shoulders, and if they take more than two steps backward or forward, or exhibit no postural response, the test is considered positive. However, the reliability and predictive value of the pull test are low due to factors such as variability in test execution and interpretation. Furthermore, the pull test solely evaluates postural reactions in response to mechanical perturbations under static conditions, failing to capture the diverse circumstances in which falls may occur. Therefore, while the pull test provides some insight into postural stability, it may not fully reflect real-world fall risk. Deformities are common in Parkinson's disease due to the prevalence of hypertonia in the flexor and adductor muscles.

One such deformity is camptocormia (Figure 2) characterized by a forward flexion of the head and trunk, shoulders positioned anteriorly, arms close to

the body, forearms flexed and internally rotated, thighs adducted, legs flexed, and feet in varus. Over time, camptocormia can lead to skeletal changes, including kyphoscoliosis.

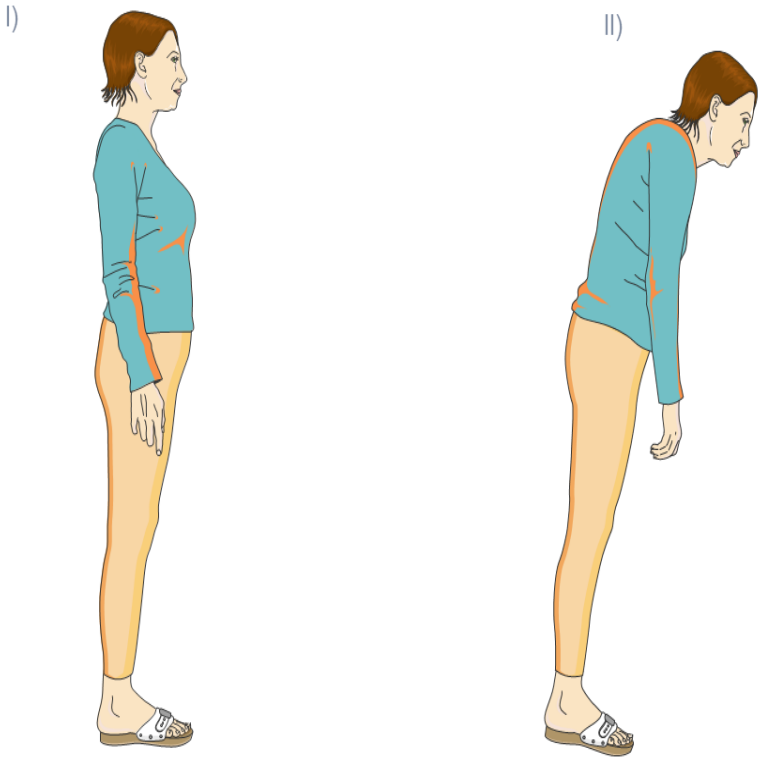

Figure 2 The figure represents a typical Camptocormic attitude. (Not Published)

I) Typical posture of a normal person without Parkinson's disease II) Typical Camptocormic posture of a Parkinsonian patient. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

Another frequent deformity is anterocollis, where there is a forward flexion of the head and neck. In some cases, patients may exhibit disproportionate anterocollis, with a more pronounced forward droop of the neck compared to the flexed posture of the trunk and limbs. Pisa syndrome, characterized by a lateral tilt in the frontal plane of the spine of at least 10°, is also typical in Parkinson's disease.

This tilt decreases when the patient is lying down or with passive movement and may precede the development of scoliosis [108].

Postural deformities can also affect the hands, with "striatal hand" presenting as metacarpophalangeal flexion, interphalangeal extension, and ulnar deviation. This deformity can cause discomfort and hinder daily activities such as writing, eating, and buttoning. Similarly, the feet may be affected by "striatal foot," marked by hyperextension of the big toe, flexion of the other toes, and ankle inversion. This deformity can impair walking, shoe wearing, and if untreated, may lead to skin ulcers and bone erosions. [109]

2.5.1.4 Walking disorder

Walking disorders in Parkinson's disease are characterized by difficulty in initiating and maintaining a steady gait, resulting in slow and short-stepped movements with the feet often shuffling along the ground.

Additionally, there is a reduction or absence of swinging movements of the upper limbs during walking.

These gait disturbances encompass two main phenomena: freezing of gait (FOG) and festination. Freezing of gait is described as brief, intermittent episodes where forward progression of the feet is significantly reduced or halted despite the intention to walk. Patients may feel as though their feet are stuck to the ground, particularly during challenging situations such as turning, navigating through narrow spaces, or approaching obstacles.

These episodes typically last a few seconds but can occasionally persist for longer durations, severely impacting the patient's independence and increasing the risk of falls.

It is noteworthy that freezing of gait is not universally present in Parkinson's patients, with only 47% experiencing this symptom, which is more common in men, those with longer disease durations, and less frequent in individuals where tremor is the dominant symptom [110].

Festination, seen in later stages of the disease, involves a progressive acceleration of gait characterized by a forward-leaning posture that leads to a constant tendency to lurch forward [111-112].

Both freezing of gait and festination significantly diminish patients' mobility, independence, and overall quality of life.

2.5.1.5 Dystonia

Dystonia, a motor symptom observed in Parkinson's disease, involves sustained muscle contractions often accompanied by abnormal movements or postures.

While it can rarely appear as a pre-diagnostic symptom, dystonia in Parkinson's disease is primarily linked to treatment, whether medical or surgical.

Prediagnostic dystonic symptoms may manifest in various ways, such as unilateral equinovarus foot positioning, flexion of the upper arm-forearm or forearm-hand, writer's cramp, oromandibular dystonia, torticollis, or combinations thereof. [113]

Typically, Parkinson's disease symptoms emerge within a decade of dystonia onset. In cases of juvenile-onset familial Parkinson's disease, dystonia commonly affects the foot, presenting symptoms akin to cramping.

Dystonia, alongside dyskinesias, often represents a significant motor complication associated with long-term therapy, usually appearing as an OFF phenomenon or peak dose dystonia. OFF dystonia typically affects the foot, while peak dose dystonia more frequently involves the neck and face.

2.5.1.6 Speech and writing disorders

Voice disorders are prevalent in Parkinson's disease, affecting 70 to 90 percent of patients, with abnormalities often detectable even in the early stages of the disease.

These disorders are part of a broader spectrum of changes affecting speech articulation, collectively known as "hypokinetic dysarthria." [114] Speech abnormalities manifest across various interconnected domains including phonation, articulation, and prosody.

In terms of phonation, there is a reduction in voice volume (hypophonia) and impairment in voice quality (dysphonia); articulation is hindered by diminished range of articulatory movements (hypokinetic articulation); and speech prosody is affected, characterized by flattened tone inflection (monotone) and loss of accent. Other features may include festination, marked by accelerated speech and hesitation during speaking [115,116].

In severe cases, palilalia may occur, involving repetitive iteration of a word or syllable. In terms of writing disorders, micrographia is often an early symptom, defined as "an impairment of fine motor skill characterized by a progressive reduction in amplitude during writing tasks." Recent research employing objective criteria has demonstrated that 63% of Parkinson's disease patients experience micrographia. [117]

Additionally, writing speed and sentence length are reduced, alongside increased interruptions and variability in movement size [118].

2.5.2 Non-motor symptoms

Non-motor symptoms are prevalent and encompass autonomic dysfunction, cognitive/neurobehavioral disorders, sensory abnormalities, and sleep disturbances [119]. These symptoms significantly impact patient management, disability, and everyday activities. They are now acknowledged as a fundamental aspect of Parkinson's disease, occurring in all patients over the course of the disease progression. [120]

2.5.2.1 Sensory abnormalities

Various sensory abnormalities are observed in Parkinson's disease. Among these, olfactory impairment is perhaps the most widely recognized, but visual abnormalities, alterations in pain perception, and paresthesias are also common [120]. Olfactory impairment affects approximately 90% of patients, often emerging early, even at the time of diagnosis.

However, a significant portion of affected individuals, more than 70%, may not be aware of their diminished sense of smell. Olfactory dysfunction may serve as an early indicator of impending motor symptoms. [121]

Pain is frequently reported in Parkinson's disease and can stem from primary sources or secondary causes such as motor fluctuations or morning dystonia.

Additionally, deep visceral pain may occur, sometimes associated with retroperitoneal fibrosis linked to specific dopaminergic agonists derived from ergot. While oral and genital pain are rare, they may still manifest in some cases [122]. Visual disturbances in Parkinson's disease encompass a wide range of issues including reduced contrast sensitivity, impaired color discrimination, convergence insufficiency, impaired stereopsis, and dry eye syndrome. Abnormalities affecting periocular structures like seborrheic blepharitis and Meibomian gland disease are also more prevalent among individuals with Parkinson's disease. Recent research has highlighted characteristic thinning of the retinal nerve fiber layer and inner retinal fovea, as well as α-synuclein deposition in retinal amacrine and ganglion cells, suggesting a multifactorial basis for visual symptoms [123].

2.5.2.2 Autonomic dysfunction

Since the inception of Parkinson's disease, autonomic dysfunction symptoms have been acknowledged as a significant component of the condition.

These encompass a range of issues including cardiovascular, sexual, bladder, gastrointestinal, and sweat gland abnormalities. [124]

The underlying pathophysiology is intricate and involves degeneration and dysfunction of nuclei responsible for autonomic functions, such as the dorsal vagal nucleus, the nucleus ambiguus, and other medullary centers like the rostral ventrolateral medulla, ventromedial medulla, and caudal raphe nuclei, which regulate sympathetic preganglionic neurons via descending pathways.

Additionally, degeneration of cholinergic, monoaminergic, and serotonergic nuclei contributes to abnormalities in modulatory effects within the central autonomic network [125]

Orthostatic hypotension stands out as the most recognized cardiovascular dysfunction, affecting nearly 60% of individuals with Parkinson's disease, although only a minority experience symptomatic manifestations

Gastrointestinal dysfunction can present in various forms, including dysphagia, gastroparesis, bacterial overgrowth in the small intestine, and constipation.

In advanced stages, inefficient swallowing may lead to drooling and potentially dangerous complications such as aspiration of food into the airway.

Constipation, reported in 80-90% of cases, is particularly noteworthy as an early symptom, often appearing 15 to 3 years before motor symptoms, emphasizing the importance of its recognition [126]. Genito-urinary

dysfunction is common, occurring in 25-50% of patients, with detrusor overactivity being the most prevalent urodynamic abnormality, resulting in urinary urgency, pollakiuria, nocturia, and urge incontinence [127].

Concerning sexual function, males may experience erectile dysfunction, difficulty achieving orgasm, or premature ejaculation (often compounded by testosterone deficiency), while females more commonly report low sexual desire, difficulty with arousal, and difficulty reaching orgasm [128].

2.5.2.3 Sleep disorders

Sleep disturbances are highly prevalent in Parkinson's disease, affecting approximately 90% of patients. [129]

They manifest in various forms, including daytime drowsiness, "sleep attacks," and nocturnal sleep disorders. Nocturnal sleep disturbances encompass insomnia, often closely linked to the illness or medications, resulting in sleep fragmentation, frequent and prolonged awakenings,

REM sleep behavior disorder (RBD), periodic limb movements, restless legs syndrome, and akathisia [130]. Among these, REM sleep behavior disorder (RBD) is the most common, affecting up to 50% of individuals with Parkinson's disease. RBD involves parasomnias occurring during REM sleep, characterized by the "acting out" of dreams.

These behaviors can range from mild muscle contractions to vocalizations to violent and complex motor actions, posing risks such as falls from bed, self-harm, or injury to partners.

Indeed, partners often notice these behaviors during sleep, as patients themselves remain unaware of most episodes. [131]

2.5.2.4 Cognitive-behavioral disorders

Both psychiatric disorders and dementia are more prevalent in Parkinson's disease compared to the general population.

Neuropsychiatric changes like anxiety and depression can emerge from the prodromal premotor phase to advanced stages of the disease and may fluctuate alongside motor symptoms. Anxiety, in particular, tends to dominate during off periods.

There is often an overlap between anxiety and depression. Recognizing psychiatric comorbidities is crucial for effective management. [134]

Cognitive decline typically occurs in the advanced stages of Parkinson's disease (PD), affecting nearly all patients who live long enough.. It is one of the most common and disabling nonmotor symptoms of PD and is associated with increased mortality. This decline also impairs social functioning, increasing the burden of care and the cost of medical treatment. [135-136]

The pathophysiology of cognitive impairment in PD is complex and likely involves the disruption of multiple neural networks. [137]

The timing, profile, and speed of cognitive decline vary widely among patients. In the early stages of the disease, most patients exhibit single-domain non amnestic cognitive decline, with impairments in visuospatial functioning, attention, or executive functions [138-140]. Impairments in language and visuospatial tests are particularly sensitive in predicting dementia [141,142]. However, cognitive decline can affect multiple domains simultaneously. [139]

To explain this heterogeneity, the "dual syndrome hypothesis" has been proposed.[143] According to this hypothesis, patients with greater dysfunction of the fronto-striatal network, modulated by dopamine, predominantly experience impairments in attention, working memory, and executive functions. In contrast, patients with posterior cortical degeneration show more significant impairments in memory, language, and visuospatial functioning due to greater cholinergic loss.

The MDS Rating Scales Review Committee has recommended the Montreal Cognitive Assessment, the Mattis Dementia Rating Scale Second Edition, and the Parkinson's Disease-Cognitive Rating Scale for cognitive monitoring [144]. These instruments adequately represent relevant cognitive domains and have been found to be reliable, valid, and sensitive to changes in Parkinson's disease.

2.6 Diagnosis

The diagnosis of Parkinson's disease primarily relies on clinical assessment, focusing on the evaluation of cardinal motor signs and symptoms.

However, diagnosis remains challenging due to the potential overlap of clinical features with other neurodegenerative conditions, and the lack of definitive tests or biomarkers. Consequently, clinical diagnostic accuracy remains suboptimal, even in cases where the disease is fully clinically manifest.

There is a need for improved identification of the prodromal phase of the disease [145]. Imaging techniques such as CT and MRI can be valuable tools in the differential diagnosis.

While MRI itself is not diagnostic for Parkinson's disease, its utility lies in excluding other potential causes such as ischemic, inflammatory, infectious, or neoplastic conditions, as well as other forms of parkinsonism. F-fluorodopa PET and DAT-scan are indirect methods used to document degeneration of nigrostriatal dopaminergic terminals. These scans visualize reduced and asymmetric uptake of striatal dopaminergic biomarkers, particularly evident in the posterior putamen, providing supportive evidence for the diagnosis of Parkinson's disease [146].

To enhance the diagnostic precision of Parkinson's disease, the International Parkinson and Movement Disorder Society has introduced a revised set of

criteria, building upon the Queen's Square Brain Bank criteria, which have been widely utilized in recent decades. [147-148]

The MDS criteria adopt a two-step approach for diagnosing Parkinson's disease. Initially, parkinsonism is defined by the presence of bradykinesia and at least one other primary motor feature (such as asymmetric resting tremor at 5Hz and/or rigidity); these features must be clearly demonstrable and not attributable to other factors.

Subsequently, once parkinsonism is diagnosed, the determination is made as to whether it is specifically attributable to Parkinson's disease. Table 2 shows the criteria for an established clinical diagnosis of Parkinson's disease.

Absence of absolute exclusion criteria	At least two supporting criteria:	No "red flags"
Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities	Clear and important beneficial response to dopaminergic therapy	Rapid progression of gait impairment requiring regular wheelchair use within 5 years of onset.
Vertical supranuclear palsy of downward gaze or selective slowing of downward vertical saccades	Presence of levodopa-induced dyskinesia	A complete absence of progression of symptoms or motor signs beyond 5 or more years, unless stability is related to treatment.
Diagnosis of probable behavioral variant of frontotemporal dementia or primary progressive aphasia	Rest tremor of a limb, documented on clinical examination	Early bulbar dysfunction: severe dysphonia, dysarthria, or severe dysphagia within the first five years.
Parkinsonian features limited to the lower limbs for more than 3 years	Positive results of at least one ancillary diagnostic test with a specificity greater than 80% for the differential diagnosis of Parkinson's disease from other parkinsonisms (olfactory loss or metaiodobenzylguanidine scintigraphy documenting cardiac sympathetic denervation).	Inspiratory respiratory dysfunction.
Treatment with a dopamine receptor blocker or an agent that depletes dopamine in a dose and time course consistent with drug-induced parkinsonism		Severe autonomic failure in the first 5 years of the disease.
Absence of observable response to high doses of levodopa despite at least moderate severity of the disease		Recurrent falls (>1/yr) due to balance impairment within 3 years of onset.
Loss of sensory cortical function (graphesthesia, stereognosis with intact primary sensory modalities), clear ideomotor apraxia of the limbs or progressive aphasia		Disproportionate anterocollis (dystonic) or contractures of the hand or feet within the first 10 years.
Normal functional neuroimaging of the presynaptic dopaminergic system		Absence of any of the common non-motor features of the disease, despite disease duration of five years.
Documentation of an alternative condition known to produce parkinsonism and plausibly related to the patient's symptoms		Alterations of the pyramidal system
		Bilateral symmetric parkinsonism.

Table 2 Criteria for clinical diagnosis of Parkinson's Disease

2.7 Course and gravity scales

The progression of Parkinson's disease exhibits considerable variability among patients. While for most individuals, the advancement is gradual and relentless, a minority may experience symptoms confinated to one side, with either mild disability or rapid progression to severe disability. Traditionally, two presentation forms are recognized:

- Hyperkinetic form: characterized primarily by tremor, often unilateral, with an earlier onset and slower progression.
- Akinetic-rigid form: typically bilateral, marked by severe rigidity and akinesia, accompanied by early gait disturbances and rapid disability progression.

Various scales are employed to assess motor impairment and disability in Parkinson's disease patients, with one of the most commonly used being the Hoehn and Yahr scale. This scale employs a simple 1 to 5 grading system to evaluate the degree of autonomy/disability in patients. Those rated 1 to 3 are considered minimally disabled and capable of leading independent lives, while grades 4 or 5 signify severe disability. Higher scores on the Hoehn and Yahr scale are often associated with increased frequency of neurocognitive disorders such as dementia, depression, and hallucinations, with patients reporting lower overall quality of life [149].

Another widely used scale for assessing Parkinson's disease severity is the Unified Parkinson's Disease Rating Scale (UPDRS).

Developed in the 1980s and later revised by specialists from the Movement Disorder Society, the UPDRS comprehensively evaluates various aspects of Parkinson's disease, encompassing both motor and non-motor symptoms' impact on daily life, as well as motor complications [150]. It consists of four parts: Part I focuses on non-motor symptoms, Part II assesses the impact of motor symptoms on daily life, Part III involves neurological motor examination, and Part IV evaluates motor complications. Each question within the UPDRS is rated on a scale of 0 to 5, reflecting varying degrees of symptom severity, with "slight" indicating minimal impact and "severe" indicating significant impairment. The complete assessment typically takes approximately 30 minutes to conduct. [151]

2.7 Pharmacological therapy

To date a definitive treatment for Parkinson's disease remains unavailable, making therapy primarily symptomatic. Guidelines advise addressing motor symptoms when they significantly affect daily functioning or diminish quality of life. Treatment strategies for Parkinson’s disease are reported in Table 3

Treatment	*Drugs*
Levodopa/Carbidopa	
MAO-B Inibitors	Selegiline,
	Rasagiline
	Safinamide
COMT inhibitors	Tolcapone
	Entacapone
	Opicapone
Dopamine agonists	Rotigotine,
	Pramipexole
	Ropinorole
	Apomorphine
Anticholinergics	Trihexiphenilide,
	Benztropine,
	Orphenadrine
	Biperiden
Amantadine	

Table 3 Farmacology treatment for Parkinson's Disease

Chapter 3

Advances Terapies

In recent decades, novel treatments have emerged to address Parkinson's disease and Essential tremor, particularly for patients with advanced stages who exhibit inadequate response to conventional therapies and endure disabling symptoms that significantly diminish their quality of life. These treatments can be categorized into pharmacological and surgical interventions, encompassing both lesional and non-lesional approaches.

- Pharmacological therapies comprise: Continuous subcutaneous infusion of Apomorphine; Continuous intestinal infusion of Duodopa gel (LCIG) for PD.
- Surgical interventions include: Magentic Resonance-guided Focused Ultrasound (MRgFUS); Deep brain stimulation (DBS) , for PD and ET.

While the administration of apomorphine infusion and levodopa/carbidopa gel is tailored exclusively to patients diagnosed with Parkinson's disease, ultrasound therapy and deep brain stimulation are recommended for individuals with either Parkinson's disease or essential tremor.

3.1 LCIG (Levodopa/carbidopa intestinal gel)

Duodopa (Levodopa/Carbidopa) continuous intestinal infusion received approval in Europe back in 2004 for managing Parkinson's disease. [120]

This formulation, also known as levodopa/carbidopa intestinal gel (LCIG), is directly administered into the proximal small intestine (jejunum) via a percutaneous endoscopic jejunostomy (PEG-J) tube. Its primary objective is to regulate the absorption rate of orally administered levodopa and counteract the delayed gastric emptying often observed in patients with Parkinson's disease, ensuring a consistent plasma concentration of levodopa. This mechanism aims to deliver levodopa to the brain at a more steady pace, mirroring a closer approximation to the body's natural physiological state.

LCIG is specifically indicated for individuals with advanced Parkinson's disease who have not responded adequately to oral levodopa treatment and suffer from severe and debilitating motor fluctuations and dyskinesias. Deciding to undergo this therapy requires careful consideration of its benefits weighed against the risks associated with dijunostomy and continuous infusion pump [153]. The placement of the PEG-J tube is conducted by an endoscopist under general anesthesia (Figure 3 a). Prior to the procedure, patients receive antibiotic prophylaxis with a single dose of cefazolin or amoxicillin/clavulanic acid.

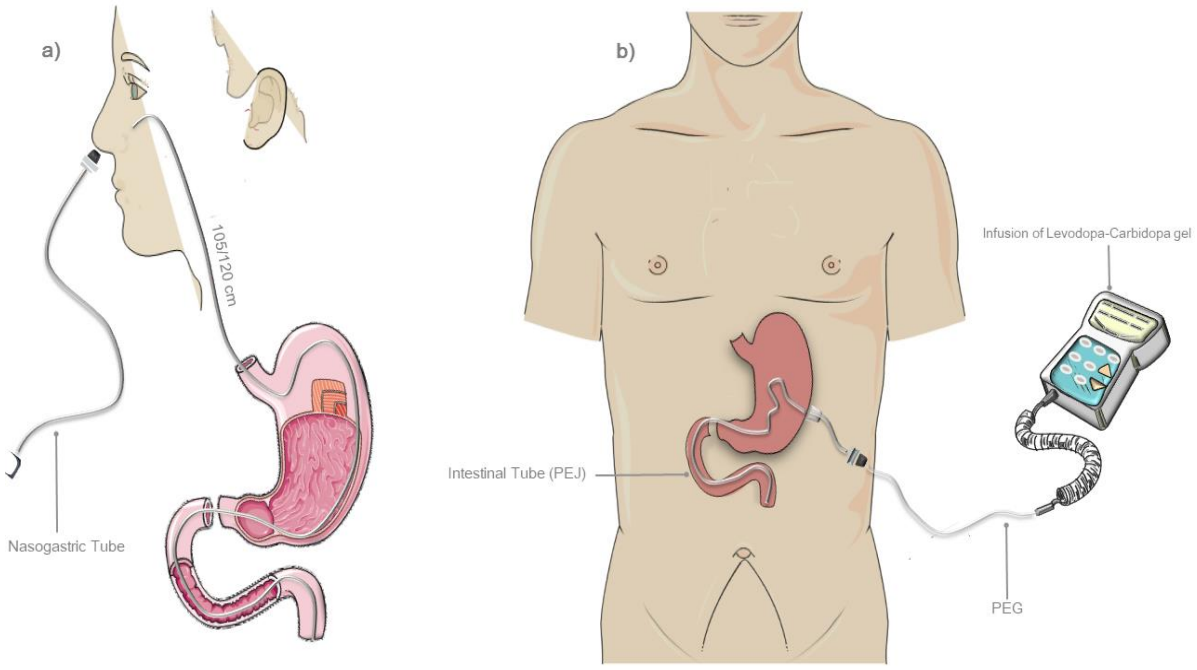

Figure 3 Treatment with Levodopa-Carbidopa intestinal gel (LCIG) infusion. (Not Published)

a) Representation of the "test" phase with temporary nasointestinal tube. This phase was performed to evaluate treatment response.

b) Representation of the Duodopa infusion system.

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3.2 Continuous Subcutaneous Apomorphine Infusion (CSAI)

The continuous administration of apomorphine represents a significant advancement in treating advanced Parkinson's disease. Figure 4

. This shift aims to circumvent hepatic metabolism limitations that compromise its bioavailability when taken orally. Presently, apomorphine is prescribed for Parkinson's disease patients experiencing severe "off" periods, motor fluctuations, dyskinesias, and symptoms unresponsive to optimized levodopa therapy. Subcutaneous administration of apomorphine is favored over oral intake for long-term use due to reduced first-pass metabolism. In comparison, intravenous administration risks apomorphine crystallization during chronic use, leading to thrombus formation [154]. Continuous infusion of apomorphine (CSAI) stands out as a vital treatment for advanced Parkinson's disease by offering sustained dopaminergic stimulation, minimizing drug response fluctuations, and preventing levodopa-induced dyskinesias [155]. Administered via a portable pump system, CSAI provides continuous dosing with the option for additional doses as needed.

Typically lasting 12 to 16 hours, the infusion is paused overnight. Dosage begins low and is gradually increased until the optimal range, typically between 4 and 7 ml/h, is achieved for most patients. [156]. CSAI is generally well tolerated, with mild to moderate side effects, less severe than alternative advanced therapies like intestinal administration of levodopa/carbidopa gel or deep brain stimulation.

Common adverse effects include injection site discomfort, skin issues, and subcutaneous nodules. Less frequent but more serious side effects encompass QT interval prolongation, hemolytic anemia, and eosinophilic syndrome [157,158]. In summary, considering its manageable side effects and substantial improvement in both motor and non-motor symptoms for patients with advanced Parkinson's disease, CSAI therapy emerges as a valuable adjunct to conventional treatment

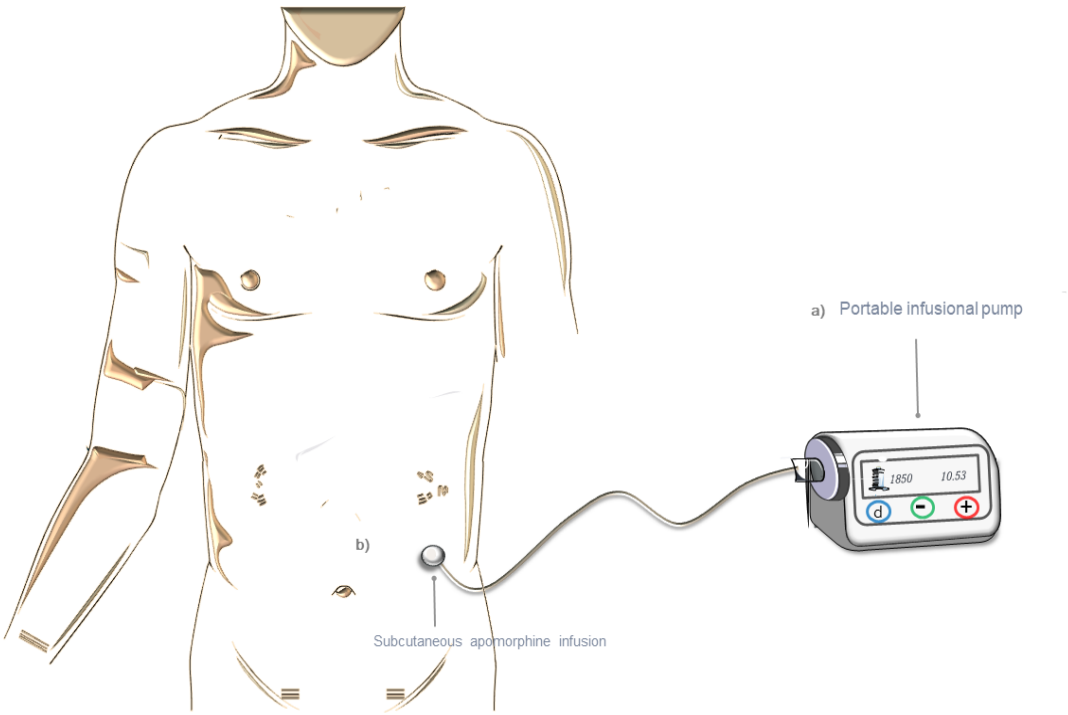

Figure 4 Treatment with Continuous Subcutaneous Apomorphine Infusion (CSAI). (Not Published)

a) Representation of the portable infusion pump.
b) Subcutaneous infusion.
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3.3 Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS)

Transcranial thalamotomy, employing high-intensity focused ultrasound guided by magnetic resonance imaging (high-intensity MRgFUS), has emerged as a novel and minimally invasive approach for ablating deep brain structures. It holds promise as an innovative treatment particularly for addressing tremors associated with Parkinson's Disease exhibiting predominant tremor-like symptoms and atypical parkinsonisms in patients unresponsive to conventional medical interventions. While pharmacological treatment is an option for managing tremors that significantly disrupt daily activities, its effectiveness is limited in approximately 50 percent of cases. [159] Initial attempts at brain ablation using high-intensity focused ultrasound (HIFU) in the 1950s, pioneered by Russel Meyers and William and Francis Fry, were constrained by the necessity of a craniotomy to establish an acoustic window. However, recent strides in transducer design, advancements in algorithms to correct magnetic wave distortion caused by the skull, and improvements in MRI technology have obviated the need for a craniotomy, thereby facilitating transcranial HIFU procedures. Moreover, precise targeting and real-time monitoring of temperature dynamics during the procedure have become attainable. [160,161]

In the treatment of tremors, HIFU is employed to ablate deep brain nuclei located within specific anatomical regions implicated in the neurofunctional circuits governing movement control, primarily within the thalamus.

The thalamus plays a pivotal role in regulating motor functions through the pallidum-thalamus-cortical (extrapyramidal system) and cerebellum-thalamus-cortical (muscle tone regulation) circuits, with the ventral intermediate nucleus (Vim) of the thalamus serving as the preferred target for patients with Parkinson's disease exhibiting tremor dominance. This technique harnesses ultrasound energy to achieve precise thermoablation in a minimally invasive manner, with MRI guidance facilitating accurate target localization, real-time monitoring of thermal ablation progression, and assessment of treatment efficacy.

Inclusion criteria:

- Previous unsuccessful treatment with a minimum of three first-line medications.
- Comprehensive neurological examination, confirming the indication.
- No controindication to undergo magnetic resonance imaging without the use of contrast medium (MRI SMDC) and cranial computed tomography (CT) scan.
- Skull Density Ratio (SDR) values equal to or greater than 0.30.
-

Main contraindications to treatment:

- Presence other brain disorders (such as brain tumors or intracranial aneurysms).
- Presence of brain implants (like shunts or electrodes).
- Occurrence of brain hemorrhage or seizures within the past year.
- Continuous use of anticoagulant medications that cannot be discontinued or existence of hematologic disorders with a high risk of bleeding.
- Presence of a pacemaker.
- Prior history of deep brain stimulation (DBS) therapy.

The procedure starts after a thorough assessment of the patient through screening neurological and neuroradiological examinations. Once compatibility with neuroimaging examinations is confirmed, hospital admission follows.

From a neuroradiological standpoint, alongside conducting a brain MRI, it is essential to assess the Skull Density Ratio (SDR). SDR values below 0.3 signify diminished ultrasound transmission across the skull, resulting in lower temperature elevation and reduced focus. SDR represents the average ratio of Hounsfield units between spongy and cortical bone of the skull. Before initiating treatment, venous access is established on the contralateral side to the targeted region. Additionally, hair is shaved to minimize ultrasound diffraction.

During the preparatory phase, as depicted in Figure 6, a stereotactic frame is employed, secured onto the skull with screws positioned anteriorly above the orbit and posteriorly to the occipital protuberance. This occurs subsequent to the subcutaneous and periosteal administration of a local anesthetic mixture.

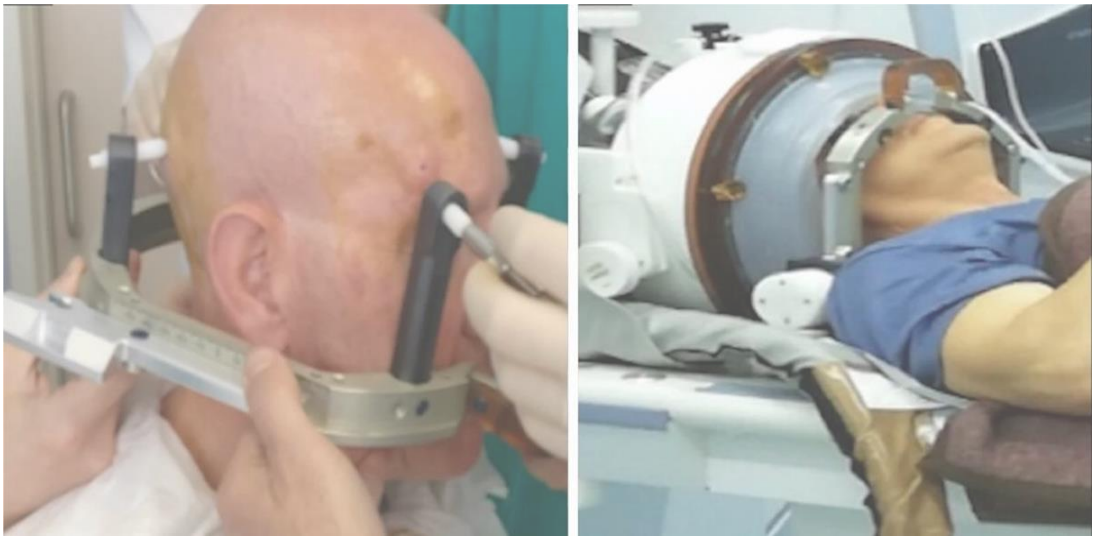

Figure 6 Stereotactic frame

Following the preparatory phase, the patient undergoes MRI placement to initiate the treatment phase.

In the initial stage, termed alignment, sonication is administered at low power and for a brief duration to ensure precise targeting of the selected region, specifically the thalamic nucleus. This alignment is verified across three planes (sagittal, axial, and coronal), with adjustments made if necessary. Temperature elevation typically ranges between 41 and 46°C.

Subsequently, during the verification phase, sonication power is incrementally escalated. This allows for a temporary alleviation of tremor symptoms and

assessment of any adverse effects. Continuous monitoring of the target ensures procedural accuracy, guided by the patient's clinical and neurological examination. Temperature elevation during this phase typically ranges from 46 to 52°C. Modifications to the focus may be made based on tremor presence, adverse events, and patient response, taking into account the somatotopic organization of the ventral intermediate nucleus (VIM) and adjacent thalamic nuclei. In the final phase, known as ablation (see Figure 7 a) there is a progressive increase in energy, duration, and total sonications. Treatment is ceased upon achieving tremor control, ensuring the temperature does not exceed 60°C. Typically, necrosis is induced through two sonications at temperatures surpassing 56°C.

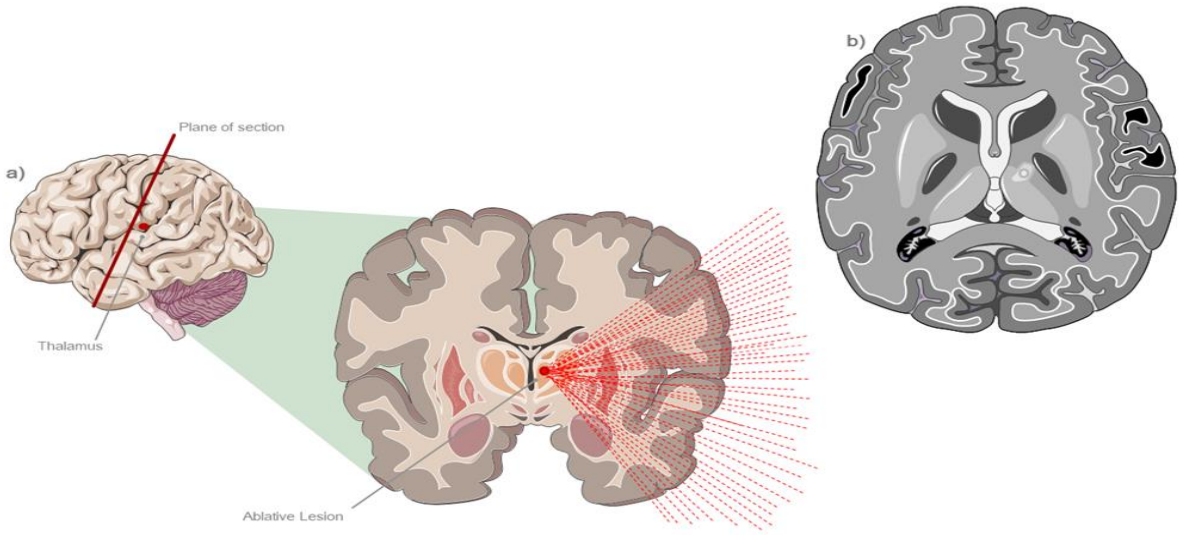

Figure 7 Treatment with Magnetic Resonance Imaging-guided Ultrasound (MRgFUS). (Not Published)

a) Ablative lesion of the left ventral intermediate thalamic nucleus (VIM).

b) Representation of a characteristic lesion of the VIM at 24-hours after treatment. The figure shows the formation of typical edema around the lesion area. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

At 24 hours post-treatment, the patient undergoes a comprehensive neurological and neuroradiological examination to monitor signs of brain edema formation and assess the treatment outcome (as depicted in Figure b). [162-165]

The primary adverse effects comprise lightheadedness, vertigo, headache, and scalp warming, which are transient and linked to the procedural process itself. Less frequent are enduring side effects, including disturbances in balance, altered sensation (such as paresthesias and dysesthesias), and motor impairments.

In the majority of cases, these effects stem from the expansion of ablation beyond the intended therapeutic site, triggered by the temporary presence of tissue edema. [166]

3.4 Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) is a surgical intervention utilized for the management of movement disorders like Parkinson's disease, dystonia, and essential tremor, achieved through the implantation of electrodes. This technique enables the regulation of dysfunctional neuronal circuits through electrical stimulation. During the 1950s and 1960s, deep brain structures were electrically stimulated to address chronic pain and psychiatric conditions.

Unlike ablative procedures, this method involved chronic stimulation of brain targets using electrodes [167].

A significant breakthrough in neuromodulation occurred in 1987, with Alim Benabid's pioneering implantation of the first DBS electrode to alleviate tremor in a patient. Subsequently, DBS has been extended to patients with Parkinson's disease, substantially enhancing the treatment outcomes for individuals resistant to conventional therapies. [168]

In Parkinson's disease, DBS targets three main brain structures:

- Ventral Intermediate Nucleus of the Thalamus (VIM): Stimulation of VIM is indicated for tremor control. This procedure is feasible across all age groups, provided the patient's overall health is good and there are no extensive areas of brain atrophy. VIM stimulation is activated during waking hours and deactivated during sleep.

- Dysarthria and balance disturbances are the primary side effects, which can be managed by adjusting the stimulation intensity. In rare instances, ataxia or tolerance to stimulation may necessitate treatment modification. Patients who do not deactivate stimulation overnight face a higher risk of adverse events.
- Globus Pallidus Internus (GPi): Stimulation of GPi is recommended for patients in advanced stages of the disease, exhibiting dyskinesias, akinesias, rigidity, and painful dystonias.

  There are no age restrictions for this intervention. Since it significantly improves dyskinesias, GPi stimulation allows patients to maintain or increase doses of dopaminergic drugs without the risk of therapy-induced complications.
- Subthalamic Nucleus (STN): STN stimulation (Figure 8) is employed in advanced Parkinson's disease cases. It demonstrates high efficacy in alleviating all motor symptoms. Favorable outcomes are observed in younger patients, levodopa responders, those with preserved cognitive function, and individuals without psychiatric comorbidities, particularly depression. Dysarthria, mood alterations, and behavioral changes are the primary side effects.

  In summary, DBS represents an advanced therapeutic approach for patients with movement disorders, offering enhanced quality of life and more effective symptom management, particularly in cases refractory to conventional treatments. [169-172]

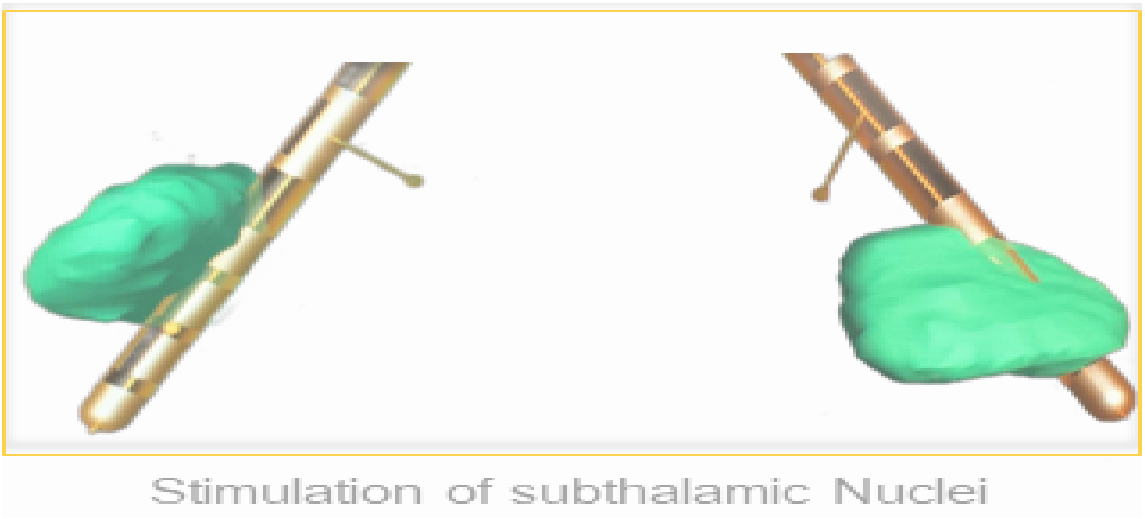

Figure 8 Electrodes placed at the level of the STN for deep brain stimulation. (Not Published)

Deep brain stimulation (DBS) represents a sophisticated surgical procedure in a state of constant evolution and refinement. Surgeons select the optimal technique based on their training, expertise, and resource availability. The prevailing approach typically involves stereotactic placement of a four-contact stimulating electrode at the desired target, alongside an implantable pulse generator (IPG) positioned subclavicularly. These components are interconnected via a subcutaneous wire. Electrode placement may be bilateral or unilateral depending on clinical requirements. Figure 9

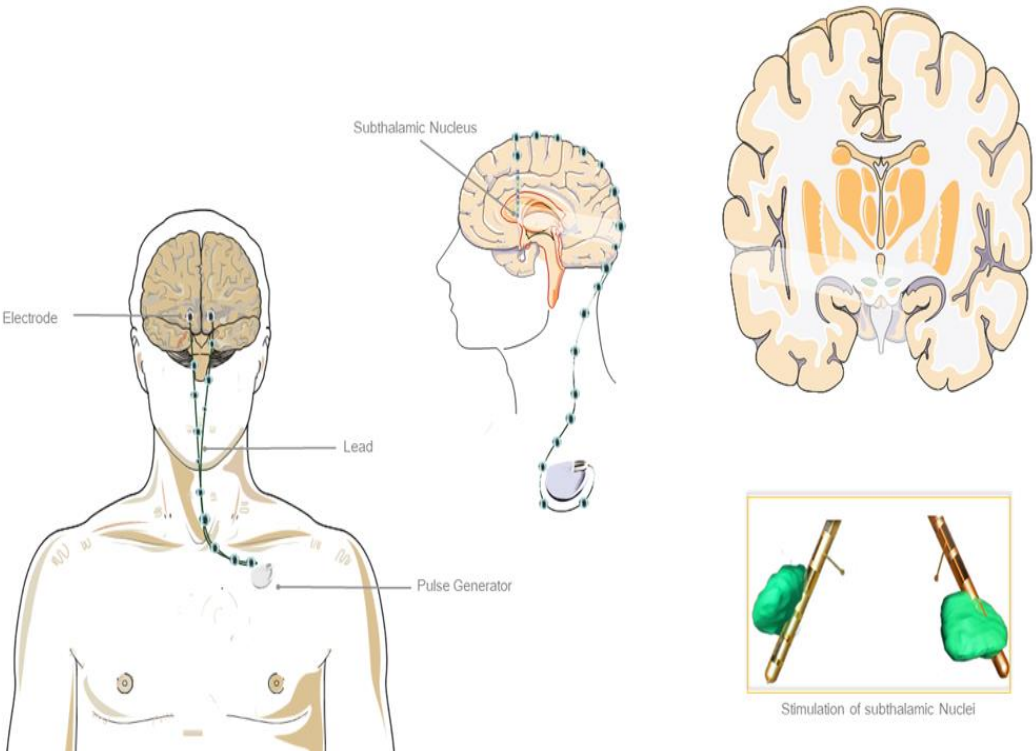

Figure 9 Deep Brain Stimulation (DBS) with subthalamic nuclei as targets (Not Published)

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Deep brain stimulation (DBS) emerges as a highly effective surgical intervention for addressing advanced-stage Parkinson's disease, particularly in managing dyskinesias and motor fluctuations. Extensive studies have demonstrated sustained improvements lasting up to 5 years, notably in motor fluctuations, through stimulation of either the subthalamic nucleus (STN) or the internal globus pallidus (GPi). Regarding tremor management, optimal outcomes are achieved through stimulation of the ventral intermediate nucleus of the thalamus (VIM).

Nevertheless, despite these encouraging findings, the progression of Parkinson's disease persists following DBS, and certain patients experience symptoms that are unresponsive to medical treatment, including freezing, postural instability, and cognitive decline. [92,97,98]

Chapter 4:

Experimental Section

4. Objective:

The COGNIFUS (COGNitive In Focused UltraSound) study aimed at investigating cognitive outcomes over a six-month period following MRgFUS thalamotomy, for tipically refractory tremor. Building upon these findings, the objective of the COGNIFUS (COGNitive in Focused UltraSound) Part 2 study was to extend this investigation to a one-year follow-up period, to validate the long-term safety and satisfaction associated with MRgFUS procedures.

4.1 Materials and Methods

4.1.1 Study design and participants

This was a prospective study involving patients undergoing MRgFUS VIM thalamotomy for medically refractory Essential Tremor (ET) and Parkinson's Disease (PD) related tremor.

All patients consecutively managed with MRgFUS for medically refractory tremor within a 1-year period were screened for the inclusion in the study. The main neurological diagnosis was performed by movement disorder specialists using the UK Brain Bank Criteria for PD and current diagnostic criteria for ET. [1,2]

Inclusion criteria for the study were:

I) Age ≥ 18 years

II) Signed informed consent to be enrolled in the study

III) Willingness to return for protocol-required follow-up visits

IV) Performance of an MRI (SMDC) and CT skull

V) SDR values ≥ 0.30.

Exclusion criteria were a well-defined history of additional neurological or psychiatric disorders, other central neurodegenerative disease other than PD, secondary parkinsonisms, presence of dementia or intellectual disability, alcohol or drug abuse, and a history of deep brain stimulation (DBS) or prior stereotactic ablation.

The study was approved by the Internal Review Board of the University of L'Aquila (n. 08/2022) and a signed informed consent to participate in the study was obtained by all the involved patients.

4.1.2 Procedures

A comprehensive clinical, neurobehavioral, and neuropsychological assessment was performed in all patients before MRgFUS thalamotomy (baseline, t0), at 6 months (t1), and one year after the procedure (t2). Main clinical variables were recorded at baseline (24–48 hours before treatment), at 6 months (t1), and during the one-year follow-up visit (t2).

4.2 Measures

4.2.1 Neuroradiological assessment

All patients underwent brain CT and MRI scans before undergoing MRgFUS treatment to assess eligibility for the procedure based on neuroimaging findings and skull density ratio (SDR) computation.

The day before the procedure, the patient's scalp was shaved and cleaned to ensure proper scalp coiling during the intervention. On the day of the procedure, after administering local anesthesia, a stereotactic frame was placed to immobilize the patient's head and facilitate precise targeting. For each patient, SDR values and sonication parameters, including Skull Area (mm2), number of active elements, target coordinates (mean, mm), Accumulated Thermal Dose (ATD) Area (mm2), Accumulated Thermal Dose (ATD) Temperature (◦C), and number of total sonications (n), were recorded.

4.2.2 Clinical assessment

Tremor severity was evaluated using the Fahn-Tolosa-Marin Clinical Rating Scale for tremor (CRST) [2], which comprises three sections assessing rest, postural, and kinetic/intention tremor amplitude in specific anatomical regions (part A); tremor during writing, drawing, and pouring tasks (part B); and impact on activities of daily living (part C), with ratings assigned on a Likert scale ranging from 0 to 4 [3,4].

Patients with PD underwent a comprehensive clinical assessment using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III [MDS-UPDRS-II and MDS-UPDRS-III] [5].

The complete MDS-UPDRS is divided into Part I, addressing non-motor experiences of daily living; Part II, addressing motor experiences of daily living; Part III, representing the motor examination; and Part IV, covering motor complications [5].

Adverse events associated with MRgFUS were categorized into two groups: MRI/ultrasound-related effects (arising from the procedure environment) and thalamotomy-related effects (resulting from the creation of a thalamic lesion).

4.2.3 Neuropsychological assessment

The neuropsychological assessment was conducted by a certified psychologist (GS) under appropriate conditions for testing, ensuring privacy, adequate lighting, and a distraction-free environment.

The assessment lasted approximately 30–40 minutes and included the following battery of tests:

- Montreal Cognitive Assessment (MOCA)
- Mini Mental State Examination (MMSE)
- Frontal Assessment Battery (FAB)
- Rey Auditory Verbal Learning Test (RAVLT)
- Single Letter-cued (phonemic) fluency test (FAS test)
- Categorical Verbal Fluency test
- Raven's Progressive Matrices (RPM)
- Hamilton Anxiety Rating Scale (HAM-A)
- Beck Depression Inventory-II (BDI-II)
- Quality of Life in Essential Tremor Questionnaire (QUEST)
- Parkinson's Disease Questionnaire-8 (PDQ-8)

4.2.3.1 Montreal Cognitive Assessment and Mini Mental State Examination

MOCA and the MMSE are brief cognitive screening tools, which provide a quick and easy global, measure of cognitive performances [6,8]. The MoCA can differentiate healthy cognitive aging from mild cognitive impairment, and it showed good reliability in PD population [9]. Attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation are some of the cognitive domains examined. Time to administer the MoCA is approximately 10 min and the total possible score is 30 points [7].

Similarly, the MMSE is a screening tool based on simple but targeted questions, that rapidly assess the neurocognitive and functional status of an individual.

It allows the evaluation of orientation (self and outward), memory, attentional capacity and ability to calculate, ability to recall new information, language and manual skills [10]. Administration of the test takes between 5 and 10 min and the total possible score is 30 points. [7]

4.2.3.2 Frontal Assessment Battery

The FAB is one of the most widely used screening tool to assess executive functions: the test investigates conceptualization processes, abstract reasoning, mental flexibility, motor programming, executive control, resistance to interference, inhibitory control, and environmental autonomy [10,11]. The FAB takes less than 10 min to administer and the total possible score is 18 points [12,13].

4.2.3.3 Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT investigates the person's ability to codify, consolidate, store and retrieve verbal information depending on the integrity of attention, concentration and short-term memory [12]. It is a short and easy to administer test and conversion tables are necessary to obtain final scores. This test includes a list of 15 concrete words with different usage frequencies and meanings, divided into three versions.

The version used for this study included the words: "Violino, Bastone, Campagna, Tempo, Lago, Notte, Brodo, Isola, Cornice, Freccia, Palazzo, Lira, Fiammifero, Barca, Parete". The patient was asked to repeat as many of the words heard as possible in any order, recording performance during five consecutive repetitions.

Account was taken not only of the quantity of words remembered, but also of any qualitative errors, such as false recognition or perseveration of the error. After an interval of 15 minutes, without repetition of the list, the patient was asked to remember as many words as possible, thus assessing the deferred retrieve ability.

4.2.3.4 Single Letter-cued (phonemic) fluency test (FAS test) and categorical Verbal Fluency test

The single letter-cued (phonemic) fluency test (FAS test) investigates executive functions and processing speed by requiring patients to name as many words as possible starting with F, A and S in 60 s, respectively [13]. The Categorical Verbal Fluency test explores lexical retrieval and production by requiring patients to say as many words as possible belonging to the ''colors'', ''animals'' and ''fruits'' categories in three different trials, which also last 60 s each [14]. In the phonemic verbal fluency test, the total score is determined by adding up the words generated across three distinct trials.

Conversely, in the semantic verbal fluency test, the final score is derived by dividing the total number of words produced by four.

4.2.3.5 Raven's Progressive Matrices (RPM)

The RPM test provides a non-verbal estimate of fluid intelligence and reasoning. It measures the problem-solving ability of subjects that is the ability to think logically and solve problems in novel situations, using logical reasoning and regardless of prior knowledge [15].

There are three versions of the test:

- The Colored Matrices (CPM) are designed to assess the cognitive level of individuals of developmental age (5-11 years), adults with intellectual retardation, and the elderly with cognitive impairment (55-93 years). This test consists of three series with 12 items of increasing difficulty: A, Ab, B. Most items in the matrices are colored, except for the last items in the B series, which are written in black ink on a white background.

- The Standard Matrices (SPM - SPM38) are the original 1938 progressive matrices used to assess adults (range 19-90). The full version includes 60 black and white plates, divided into 5 series (A, B, C, D, E). In each table, the subject must select, from 6 or 8 alternatives, the stimulus that completes a configuration displayed at the top of the table (score range 0-60). The abbreviated version uses only the first 4 sets of tables (A, B, C, D).

- Advanced Matrices (APM - PM47) are used to identify Plus Dotation (intellectual ability significantly above average). The protocol consists of 2 sets

and 48 items: the first contains 12 items; the second 36 items. The items are drawn in black on a white background.

4.2.3.6 Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A was among the earliest tools devised for assessing the intensity of anxiety symptoms and continues to be extensively utilized in clinical and research environments today.

Comprising 14 items, each delineated by a symptom cluster, the scale evaluates both psychological anxiety (mental restlessness and emotional distress) and physiological anxiety (physical manifestations associated with anxiety). Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe. [16]

4.2.3.7 Beck Depression Inventory-II (BDI-II)

The Beck Depression Inventory-II (BDI-II) is a test that is used to assess the presence of depression and its severity, designed to be administered to people ≥13 years of age. It consists of a set of 21 questions exploring depressive symptoms, which the patient is asked to answer referring to the previous two weeks.

The score for each item ranges between 0 and 3, with the total score being categorized into four groups: no depression (0-13), mild depression (14-19), moderate depression (20-28) and severe depression (29-63). [17]

4.2.3.8 Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a 30 items questionnaire divided into 5 domains (Communication, Work and Finances, Hobbies and Leisure, Physical and Psychosocial) which explore how tremor affects perceived quality of life based on independence in daily living, emotional well-being, social inclusion and employability [18].

4.2.3.9 Parkinson's Disease Questionnaire-8 (PDQ-8)

The 8-item version of the Parkinson's disease questionnaire (PDQ-8) is a shortened version of the 39-item Parkinson's disease questionnaire (PDQ-39) for quality of life.

This tool comprises eight questions derived from various domains of the PDQ-39: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and physical discomfort.

Each question is rated on a scale of 0 to 4, with the following scoring criteria: Never = 0, Occasionally = 1, Sometimes = 2, Often = 3, Always = 4. A higher total score signifies a poorer quality of life [19].

Table 3 shows the range score and cut-off values of all tests.

	Neuropsychological Assessment	*Range score*	*Cut-off*
Cognitive screening tools	*Mini Mental State Examination (MMSE)*	*0-30*	*23.80*
	Montreal Cognitive Assessment (MOCA)	*0-30*	*≥26*
Frontal Functions	*Frontal Assessment Battery (FAB)*	*0-18*	*12*
Mnestic Functions	*Rey Auditory Verbal Learning Test R.I (RAVLT R.I)*	*0-75*	*28.53*
	Rey Auditory Verbal Learning Test R.D (RAVLT R.D)	*0-15*	*4.69*
Language	*Single letter-cued (phonemic) fluency test*	-	*17.35*
	Single letter-cued (semantic) fluency test	-	*7.25*
Abstract reasoning	*Raven's Progressive Matrices*	*0-36*	*18.96*
Mood Domains	*Hamilton-Anxiety Rating Scale (HAM-A)*	*0-56*	-
	Beck Depression Inventory-II (BDI-II)	*0-63*	-
Quality of Life (QoL)	*Quality of life in Essential Tremor Questionnaire (QUEST)*	*0-120*	-
	Parkinson's Disease Questionnaire-8 (PDQ-8)	*0-32*	-

Table 3 Range score and cut-off values of all test.

4.2.4 Neuroradiological assessment and MRgFUS treatment

All patients underwent brain CT and MRI scans prior to MRgFUS treatment. CT images were obtained using a 320-row scanner (Aquilion ONE, Toshiba), utilizing a pure axial plane and providing full skull coverage (parameters: 120 kV, 220 mA, 1 mm slice thickness, bone filter reconstructions). MRI examinations were conducted on a 3T scanner (MR750w, GE Healthcare), encompassing a protocol comprising FLAIR, GRE, SWI, and DWI sequences on axial planes, as well as T2 sequences on coronal and axial planes. Additionally, a volumetric T1 3D IR FSPGR (BRAVO) sequence was employed (parameters: 1 mm slice thickness, TR 8.5, frequency FOV 25.6, phase FOV 0.8). The same MRI protocol was utilized to assess the thalamic lesion on the day following the procedure (see Figure 10).

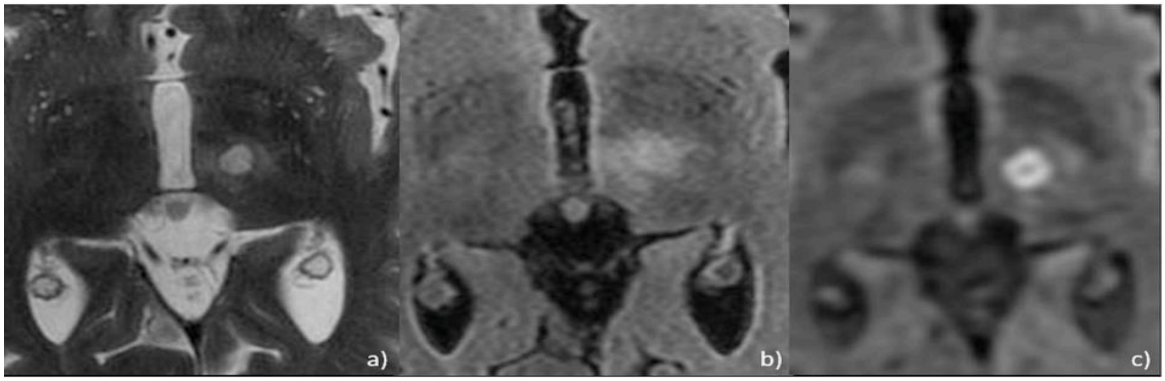

Figure 10 Postprocedural axial MRI slices depicting a left thalamotomy lesion in T2 (a), FLAIR (b) and DWI (c) sequences. The enrolled patients underwent unilateral ablation of the Ventral Intermediate Nucleus (Vim), located contralateral to the side exhibiting the most symptomatic or disabling symptoms, utilizing MRgFUS. All procedures were conducted at our

institution using a Neuro ExAblate machine (NeuroAblate 4000, InSightec Ltd, Israel).

During the post-procedural MRI evaluation, thalamotomy lesion size was assessed by a radiologist specializing in brain imaging. Measurements were conducted using the ruler tool in the PACS system on axial images of T2 sequences, focusing on the largest latero-lateral diameter. For each patient, MRI follow-up was conducted at six months and one year post-treatment. Figure 11 visually depicts the progression of a typical lesion on MRI at 24 hours, 6 months, and 1 year after the procedure.

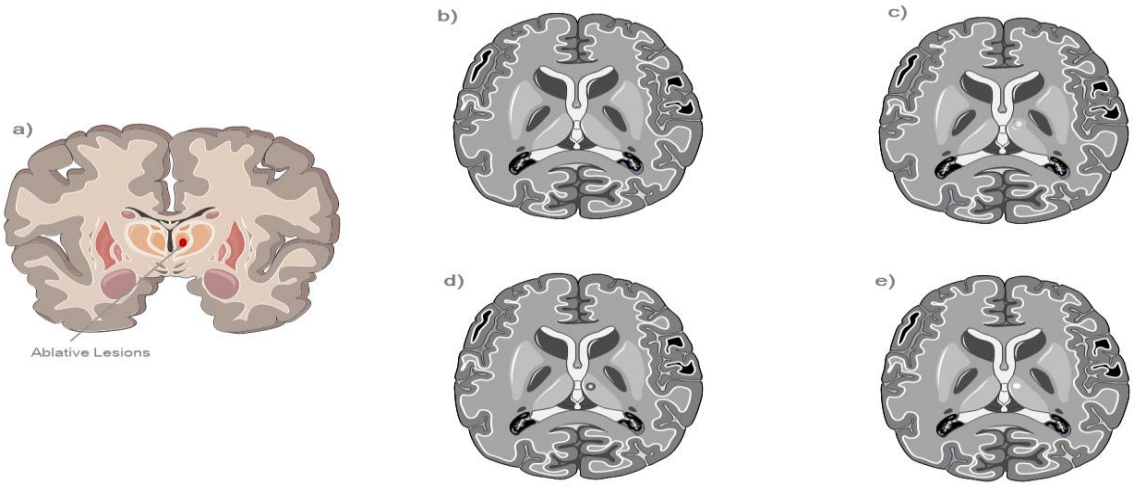

Figure 11 Evolution of a typical lesion on MRI at 24 hours, 6 months, and 1 year after the procedure: a) Ablative Lesion of Ventral Intermediate Nucleus (VIM); b) A typical MRI sequence prior to ultrasound treatment; c) Representation of a characteristic lesion of the VIM at 24-hours after treatment.; d) Figure C depicts a standard MRI T2-weighted sequence obtained six months post-treatment; e) Representation of a typical left ventral intermediate nucleus lesion one-year post-treatment In Figures C and D, a hypointense lesion characteristic of the ventral intermediate nucleus is evident. The Figure was partly

generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.4

4.3 Statistical analysis

To compare preoperative and postoperative scores, we employed either a paired T-test or a Wilcoxon signed-rank test, depending on the normal distribution status of the data. Pearson and Spearman correlation coefficients were calculated to examine associations between motor tests and neuropsychological or neurobehavioral tests. Repeated measures ANOVA was used to analyze data within the same subjects. Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequency or percentage. Results were considered statistically significant if they exceeded an alpha level of 0.003, which was adjusted using the Bonferroni correction for the number of tests (0.05/14). Statistical analyses were performed using JAMOVI 2.2.24 software.

4.4 Results Research I: Cognitive outcomes after Focused Ultrasound thalamotomy for tremor: results from the COGNIFUS (COGNitive In Focused UltraSound) study. (Parkinsonism and Related Disorders 106 (2023) 105230)

Sixty-two patients initially met the eligibility criteria and were included in the study. However, 22 patients were unable to participate in the six-month follow-up assessment due to the Covid-19 pandemic, resulting in a final sample size of 40 patients (38 males, 2 females; mean age±SD 67.7±10.7 years; mean disease duration±SD 9.3±5.6 years), who completed the entire clinical,

neurobehavioral, and neuropsychological assessment at both baseline and at the 6-month follow-up.

Among the participants, 22 were diagnosed with ET (mean age±SD 69.5±10.0 years; mean disease duration 13.10±10.02 years; mean education 9.68±3.61 years), and 18 were diagnosed with PD (mean age±SD 65.4±11.4 years; mean disease duration 7.80±4.63 years; mean education 10.39±3.80 years).

Thirty-one patients underwent a left VIM thalamotomy, while the remaining patients underwent a right VIM thalamotomy. The mean initial coordinates for Vim targeting were 7.46 mm anterior to the posterior commissure, 14.16 mm laterally from the midline, and 1.14 mm above the AC-PC line. Due to incomplete clinical response during treatment, adjustments to target coordinates were necessary, with an average total of 1.97±2.84 shifts. Further details on procedural and imaging parameters can be found in Table 4.

Procedural and imaging parameters of MRgFUS.

Parameter	Mean ± SD
SDR	0.43 ± 0.07
Skull Area (mm2)	335.67 ± 35.25
Accumulated Thermal Dose (ATD) Area (mm2)	16.69 ± 7.77
Accumulated Thermal Dose (ATD) Temperature (∘C)	54.42 ± 1.90
Elements (n)	918.67 ± 42.44
Sonications (n)	11.06 ± 3.87
Power (W)	749.08 ± 93.41
Target coordinates (mean, mm)	7.46AP-14.16LL-1.14CC
Target Movements	1.97 ± 2.84
Energy (J)	13935.14 ± 77707.55
Temperature (∘C)	61.35 ± 4.20
Sonication Duration (s)	21 ± 8.60
Thalamotomy lesion size (mm, LL)	7.45 ± 1.52

Table 4 Procedural and imaging parameters of MRgFUS

In Table 5, it is evident that there was a notable improvement in anxiety levels, as indicated by the HAM-A rating scale (5.36 ± 3.80 vs 2.54 ± 3.28, $p < 0.001$), across the entire sample following MRgFUS thalamotomy. Furthermore, significant enhancements were observed in overall cognitive functions, as evidenced by improvements in MMSE scores (25.93 ± 3.76 vs 27.54 ± 2.46, p 0.003) and MOCA scores (22.80±4.08 vs 24.48±3.13, $p < 0.001$). However, no significant alterations were found in preoperative and postoperative scores across specific domains exploring mood, frontal and executive functions, verbal fluency and memory, as well as in abstract reasoning and problem-solving abilities. Additionally, Figure 12 illustrates that the CRST total score (from 35.79±14.39 to 23.03±10.95; $p < 0.001$) and all CRST subparts (Part A from

9.91±6.06 to 6.32±3.53, $p < 0.001$; Part B from 17.06±7.17 to 12.16±5.35, $p < 0.001$; Part C from 9.06±5.70 to 4.68±4.55 $p < 0.001$) exhibited significant improvements at six months post MRgFUS thalamotomy for the entire sample.

Neuropsychological tests	Baseline	6-month follow-up	p-value
Mini Mental State Examination	25.93 ± 3.76	27.54 ± 2.46	0.003
Montreal Cognitive Assessment	22.80 ± 4.08	24.48 ± 3.13	<0.001
Frontal Assessment Battery	14.50 ± 3.17	14.88 ± 3.33	0.140
Single letter-cued (phonemic) fluency test	25.69 ± 10.81	27.76 ± 12.12	0.342
Single letter-cued (semantic) fluency test	9.94 ± 2.46	10.78 ± 3.17	0.102
Rey Auditory Verbal Learning Test R. I	30.59 ± 8.91	33.04 ± 9.99	0.032
Rey Auditory Verbal Learning Test R. D	5.17 ± 3.22	6.29 ± 4.22	0.122
Raven's Progressive Matrices	28.54 ± 6.33	29.36 ± 4.70	0.393
Hamilton Anxiety rating scale	5.36 ± 3.80	2.54 ± 3.28	<0.001
Beck Depression Inventory-II	2.90 ± 3.24	1.38 ± 1.89	0.007

Table 5 Changes in neuropsychological and neurobehavioral scores between baseline and 6-month follow-up for the whole sample

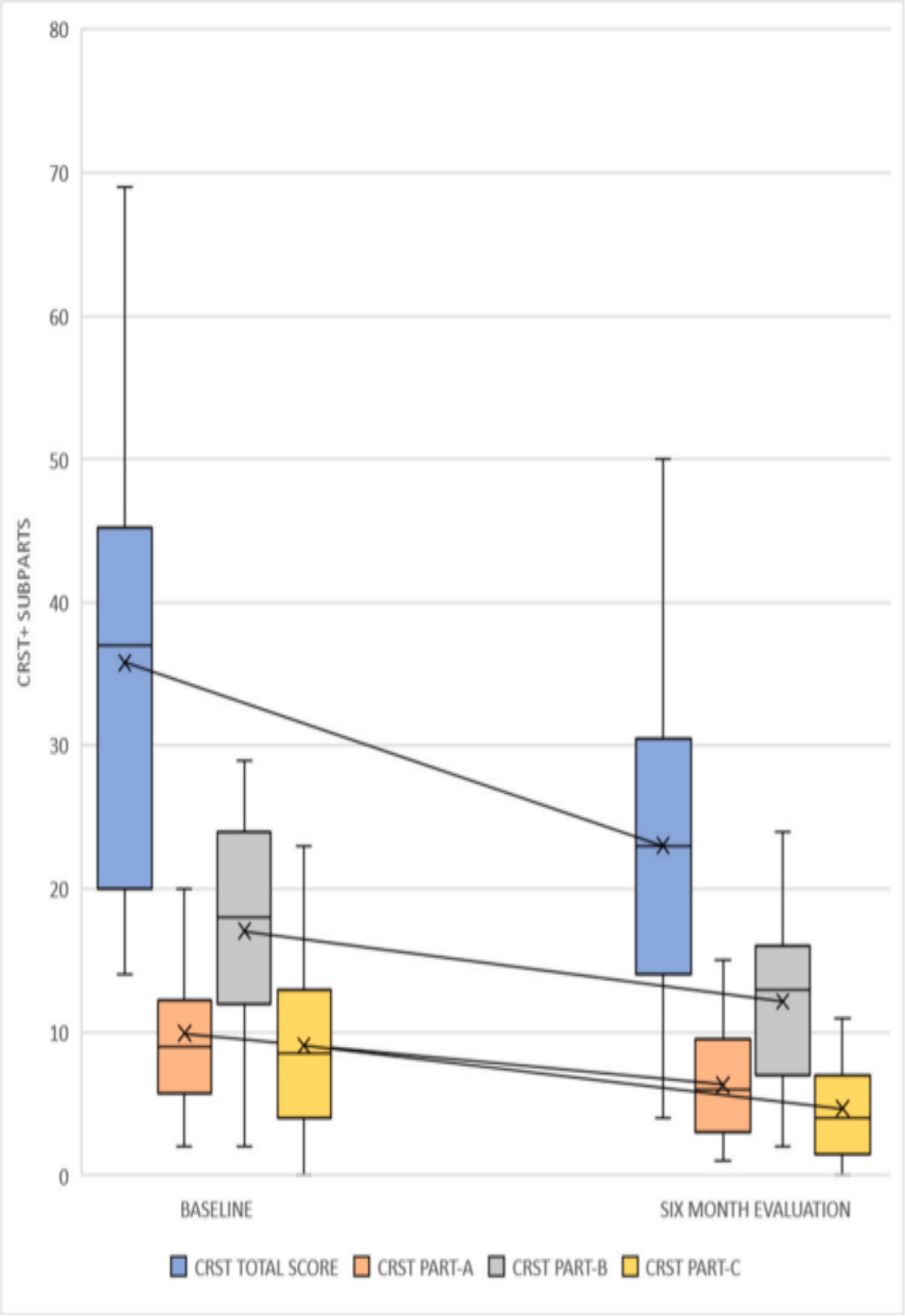

Figure 12 Clinical Rating Scale for Tremor (CRST): total and single parts (A + B + C) changes at six months.

Table 6 shows that both patients with ET and PD-related tremor experienced an enhancement in their quality-of-life following MRgFUS thalamotomy, as evidenced by the QUEST score (36.14±12.91 vs 5.14±6.90, p < 0.001) for ET patients and the PDQ-8 score (5.61±4.65 vs 1.39±2.33, p 0.001) for PD patients. Moreover, PD patients exhibited a significant improvement in the overall cognitive status, as reflected by the MOCA scores (22.56±4.10 vs 23.94±3.65, p 0.003). However, no significant changes were observed in other cognitive and behavioral domains for both ET and PD patients when considered separately. Furthermore, in PD patients, the MDS-UPDRS-III total score did not demonstrate a significant improvement at six months post MRgFUS thalamotomy (from 30.00±13.73 to 27.08±11.39, p= 0.284). Nevertheless, a relevant improvement was observed in subitems specifically addressing tremor symptoms.

	ET			PD		
Neuropsychological tests	Baseline	6-month follow-up	p-value	Baseline	6-month follow-up	p-value
Mini Mental State Examination	26.12 ± 3.82	27.72 ± 2.53	0.012	25.70 ± 3.78	27.31 ± 2.44	0.072
Montreal Cognitive Assessment	23.00 ± 4.15	24.91 ± 2.65	0.016	22.56 ± 4.10	23.94 ± 3.65	0.003
Frontal Assessment Battery	15.05 ± 3.01	15.31 ± 2.90	0.419	13.83 ± 3.31	14.33 ± 3.80	0.189
Single letter-cued (phonemic) fluency test	27.22 ± 9.29	28.40 ± 10.99	0.389	26.04 ± 12.68	26.98 ± 13.67	0.628
Single letter-cued (semantic) fluency test	10.68 ± 2.26	11.44 ± 3.00	0.153	9,04 ± 2.46	9.97 ± 3.27	0.333
Rey Auditory Verbal Learning Test R.I	30.50 ± 9.36	33.13 ± 10.52	0.148	30.56 ± 8.36	32.94 ± 9.57	0.093
Rey Auditory Verbal Learning Test R.D	5.53 ± 2.76	6.35 ± 2.47	0.134	4.73 ± 3.74	6.21 ± 5.77	0.324
Raven's Progressive Matrices	28.79 ± 7.53	30.31 ± 5.04	0.239	28.23 ± 4.66	28.19 ± 4.09	0.959
Hamilton Anxiety rating scale	5.00 ± 3.72	2.71 ± 4.14	0.018	5.50 ± 4.07	2.33 ± 1.94	0.004
Beck Depression Inventory-II	3.00 ± 3.66	1.18 ± 1.86	0.017	2.78 ± 2.75	1.61 ± 1.94	0.156
QUEST	36.14 ± 12.91	5,14 ± 6,90	<0.001	-	-	-
Parkinson's disease Questionnaire-8 (PDQ-8)	-	-	-	5,61 ± 4,65	1,39 ± 2,33	0.001

Table 6 Changes in neuropsychological and neurobehavioral scores between baseline and 6-month follow-up for ET and PD.

When analyzing neuropsychological and neurobehavioral outcomes according to the treatment side (right/left), significant improvements were observed in various measures. Specifically, a left VIM lesion correlated with significant enhancements in MOCA (22.51±3.53 to 24.06±2.98, $p < 0.001$), MMSE (25.6±3.87 to 27.73±2.38, $p < 0.001$), HAM-A (5.19±3.88 to 1.87±2.14, $p < 0.001$), and QUEST (37.0±13.99 to 5.50±7.35, $p < 0.001$) scores. Similarly, a right VIM lesion resulted in a significant improvement in QUEST scores (29.16±7.05 to 2.33±4.08, $p < 0.001$).

When exploring correlations between motor tests and neuropsychological or neurobehavioral assessments, no significant correlations were observed between total CRST scores and neuropsychological or neurobehavioral scores at both baseline and at the 6-month follow-up. However, a strong negative correlation was noted between baseline MDS-UPDRS-III and Raven's Progressive Matrices scores ($r = -0.886$; $p < 0.01$), suggesting that patients with greater motor impairment may show poorer abilities in abstract reasoning. Additionally, a moderate positive correlation was found between 6-month CRST subpart C and 6-month MMSE scores ($r = 0.389$; $p = 0.015$), indicating a potential improvement in overall cognitive status in patients with reduced tremor interference in activities of daily living.

Regarding adverse events, MRI/ultrasound-related effects included dizziness (n=21, 52.5%), scalp burning (n=16, 40%), nausea (n=8, 20%), headache (n=6, 15%), and vagal reaction (n=2, 5%).

Thalamotomy-related complications were reported in five patients, including contralateral weakness (n=3, 7.5%), dysgeusia (n=1, 2.5%), and gait instability (n=1, 2.5%), with gradual improvement observed over three months following MRgFUS thalamotomy.

4.5 Results research II: Cognitive safety of Focused ultrasound thalamotomy for tremor: 1-year follow-up results of the COGNIFUS (COGNitive in Focused UltraSound) Part 2 study (Published in Front in Neurol. 2024: 17:15:1395282.).

A total of 50 patients (76% males; mean age±SD 69.0 ± 8.56 years; mean disease duration±SD 12.13±12.59 years; mean education±SD 9.58±3.9 years) completed the clinical, neurobehavioral, and neuropsychological assessments at baseline, 6 months, and at the 1-year follow-up visit. The clinical indication for thalamotomy under MRgFUS guidance was essential tremor (ET) in 28 patients (mean age±SD 69.04± 8.0 years, mean disease duration 15.41±15.0 years, mean education 9.43± 3.95 years) and PD-related tremor in 22 patients (mean age±SD 68.95 ± 9.42 years, mean disease 7.90±6.85 years, mean education 9.77±3.91 years). In both the clinical conditions, tremor was found to be unresponsive to medical therapy or pharmacological treatment was no longer tolerable due to adverse effects.

A left VIM thalamotomy was performed in 43 patients, and a right VIM thalamotomy was performed in the remaining patients.

4.5.1 Tremor Improvement

Considering the entire sample without subgroup differentiation, significant improvements were observed in the CRST total score at both 6 months (42.94±13.67 to 27.02±11.41; post-hoc, $p < 0.001$) and 1 year (42.94±13.67 to 28.68±9.85; post-hoc, $p < 0.001$) following MRgFUS treatment (Figure 13 a).

Conversely, the postoperative MDS-UPDRS-III total score did not show significant improvement at either six months (31.23±13.50 to 28.71±10.40; post-hoc, $p= 0.577$) or 1 year (31.23±13.50 to 30.90±9.46; post-hoc, $p=1.000$) following the treatment.

Stratification of the entire sample by clinical diagnosis revealed significant improvements in total CRST score among both PD ($p < 0.001$) and ET ($p < 0.001$) patients at 6 months and at 1 year after the treatment (Figure 13 b-c).

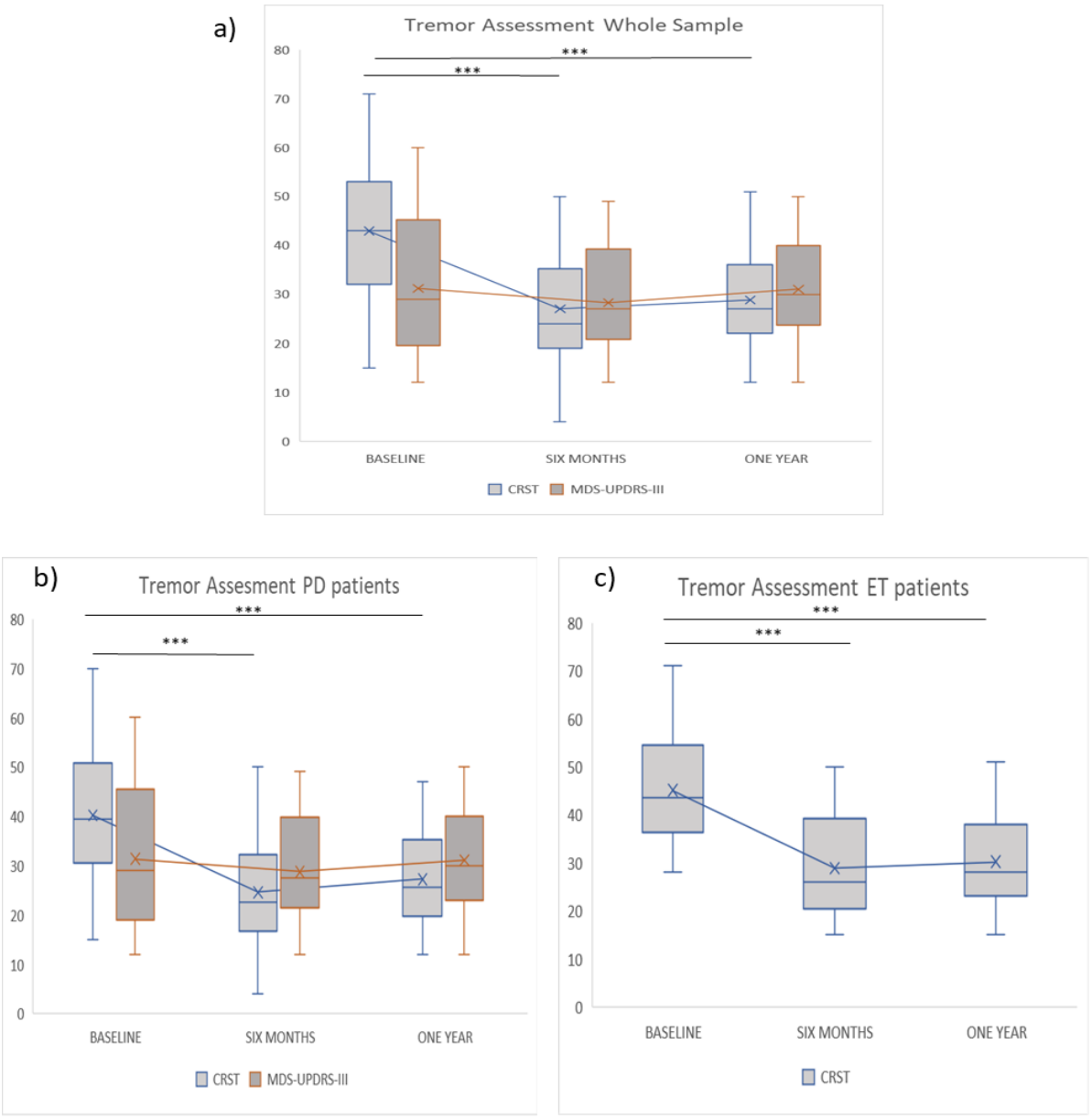

Figure 13 (a-c): Evaluation about tremor assessment at baseline, six months and 1 year follow-up.

4.5.2 Cognitive and behavioral changes

When examining the whole sample without subgroup differentiations, relevant changes in behavioral and cognitive domains were observed at both the 6-month and the 1-year follow-up assessment.

At 6 months post-treatment, statistically significant improvements were recognised in anxiety levels (HAM-A: 5.66 ± 5.02 vs. 2.70 ± 4.09, $p < 0.001$), as well as in cognitive domains such as memory (RAVLT: immediate recall 31.76 ± 7.60 vs. 35.51 ± 8.38, $p < 0.001$; RAVLT: delayed recall 5.57 ± 2.75 vs. 7.03 ± 3.85, $p < 0.001$) and frontal functions (14.24 ± 3.04 vs. 15.24 ± 2.38, $p = 0.003$). Similarly, at the 1-year follow-up following treatment, improvements were detected in anxiety and mood levels (HAM-A: 5.66 ± 5.02 vs. 2.69 ± 3.76, $p < 0.001$; BDI-II: 3.74 ± 3.80 vs. 1.80 ± 2.78, $p = 0.001$) and memory domains (RAVLT: immediate recall 31.76 ± 7.60 vs. 35.38 ± 7.72, $p = 0.001$). A comparison between mean scores is illustrated in Figure 14 (a-e). Additionally, quality of life showed an improvement both at 6 months (QUEST: 35.00 ± 12.08 vs. 8.93 ± 9.86, $p < 0.001$; PDQ-8: 7.86 ± 3.10 vs. 3.10 ± 1.52, $p < 0.001$) and at 1 year (QUEST: 35.00 ± 12.08 vs. 9.03 ± 10.64, $p < 0.001$; PDQ-8: 7.86 ± 3.10 vs. 3.09 ± 2.29, $p < 0.001$) following the treatment (Figure 14 f-g). However, psychometric tests assessing executive functions, verbal fluency, abstract reasoning, and problem-solving abilities showed no significant changes across multiple evaluations (Table 7).

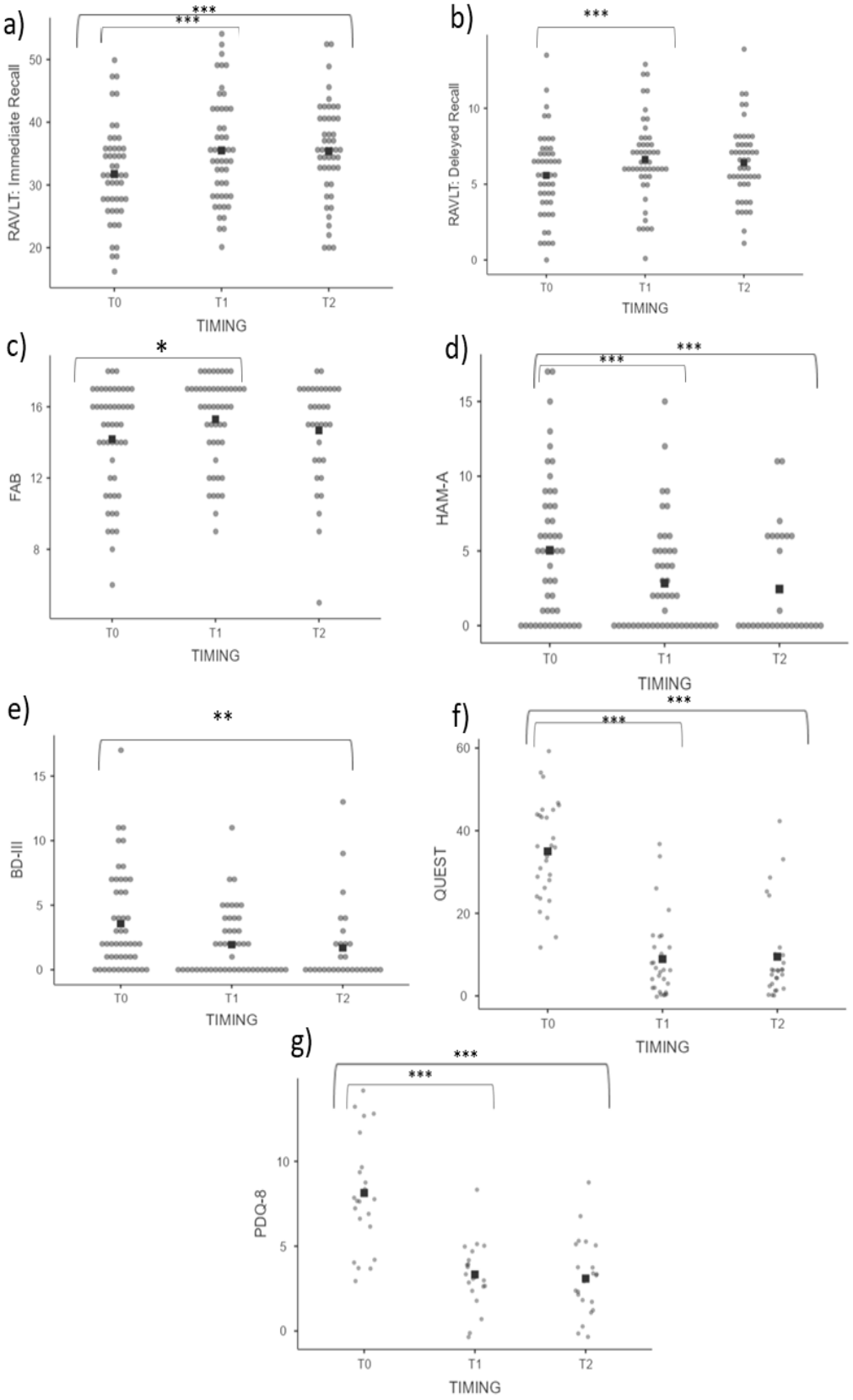

Figure 14 (a-g) Pre and postoperative scores on neuropsychological assessment of the whole sample.

Neuropsychological and Neurobehavioral tests	Baseline	6-months follow-up	1 year follow-up	p-value 6 months	p-value 1 year
Mini Mental State Examination	27.38±2.39	28.29±1.70	28.33±1.69	0.012	0.005
Montreal Cognitive Assessment	23.23±4.93	23.78±3.62	23.90±3.63	0.053	0.004
Frontal Assessment Battery	14.24±3.04	15.24±2.38	15.16±2.74	0.003	0.023
Single letter-cued (phonemic) fluency test	27.30±9.76	28.32±10.38	28.85±9.62	0.336	0.090
Single letter-cued (semantic) fluency test	10.42±2.70	10.50±2.77	10.47±2.85	0.774	0.908
Rey Auditory Verbal Learning Test R.I	31.76±7.60	35.51±8.38	35.38±7.72	<001	0.001
Rey Auditory Verbal Learning Test R.D	5.57±2.75	7.03±3.85	6.41±2.48	<001	0.011
Raven's Progressive Matrices	28.66±±4.72	28.90±5.15	28.86±5.15	0.460	0.686
Hamilton Anxiety rating scale	5.66±5.02	2.70±4.09	2.26±3.76	<001	<001
Beck Depression Inventory-II	3.74±3.80	1.90±2.70	1.80±2.78	0.006	<001
Quality of life in Essential Tremor Questionnaire	35.00±12.08	8.93±9.86	9.03±10.64	<001	<001
Parkinson's disease Questionnaire-8 (PDQ-8)	7.86±3.10	3.10±1.52	3.09±2.29	<001	<001

Table 7 Changes in neuropsychological and neurobehavioral scores across baseline, 6-months and 1 year follow-up for the whole sample.

When stratifying the whole sample by subgroups, patients with PD showed improvements in anxiety levels (HAM-A: 6.14 ± 4.51 vs. 2.55 ± 2.91, $p = 0.002$) and quality of life (PDQ-8: 8.10 ± 2.97 vs. 3.11 ± 1.56, $p < 0.001$) at the 6-month follow-up following the procedure. These improvements in quality of life persisted at the 1-year follow-up (PDQ-8: 8.10 ± 2.97 vs. 3.10 ± 2.34, $p < 0.001$), along with improvements in mood (BDI-II: 4.73 ± 3.30 vs. 1.68 ± 2.43, $p = 0.003$). (Figure 15)

On the other hand, patients with ET experienced improvements in anxiety levels (HAM-A: 5.29 ± 5.44 vs. 2.50 ± 4.76, $p = 0.001$), quality of life (QUEST: 34.93 ± 12.54 vs. 8.85 ± 10.22, $p < 0.001$), and memory domains (RAVLT: immediate recall 31.25 ± 7.31 vs. 36.28 ± 7.66, $p = 0.001$; RAVLT: delayed recall 5.60 ± 2.21 vs. 7.01 ± 2.10, $p < 0.001$) at the 6-month post-procedure assessment. Furthermore, ET patients showed improvements in memory domains (RAVLT: immediate recall 31.25 ± 7.31 vs. 36.73 ± 6.26, $p < 0.001$; RAVLT: delayed recall 5.60 ± 2.21 vs. 7.02 ± 1.73, $p < 0.001$) and quality of life (QUEST: 34.93 ± 12.54 vs. 9.77 ± 11.20, $p < 0.001$) at the 1-year follow-up after MRgFUS treatment. (Figure 16)

The detailed results are presented in Table 8

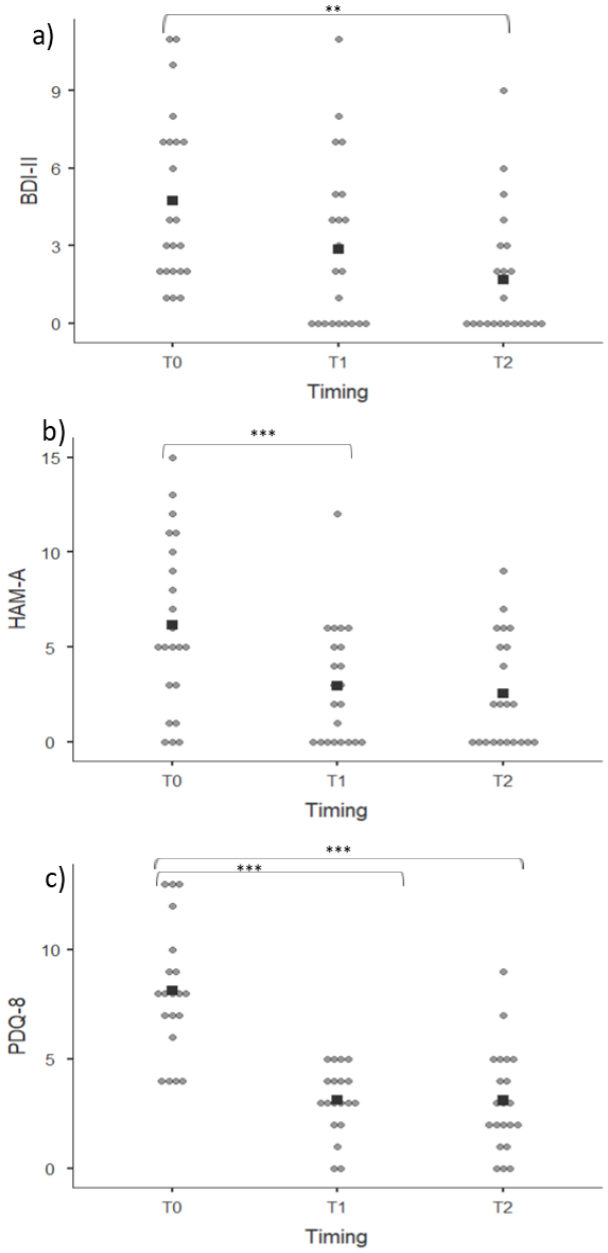

Figure 15 (a-c): Statistically significant changes in neuropsychological and neurobehavioral scores following the procedure in PD patients. Asterisks indicate significant p value (***<0.001, **0.003).

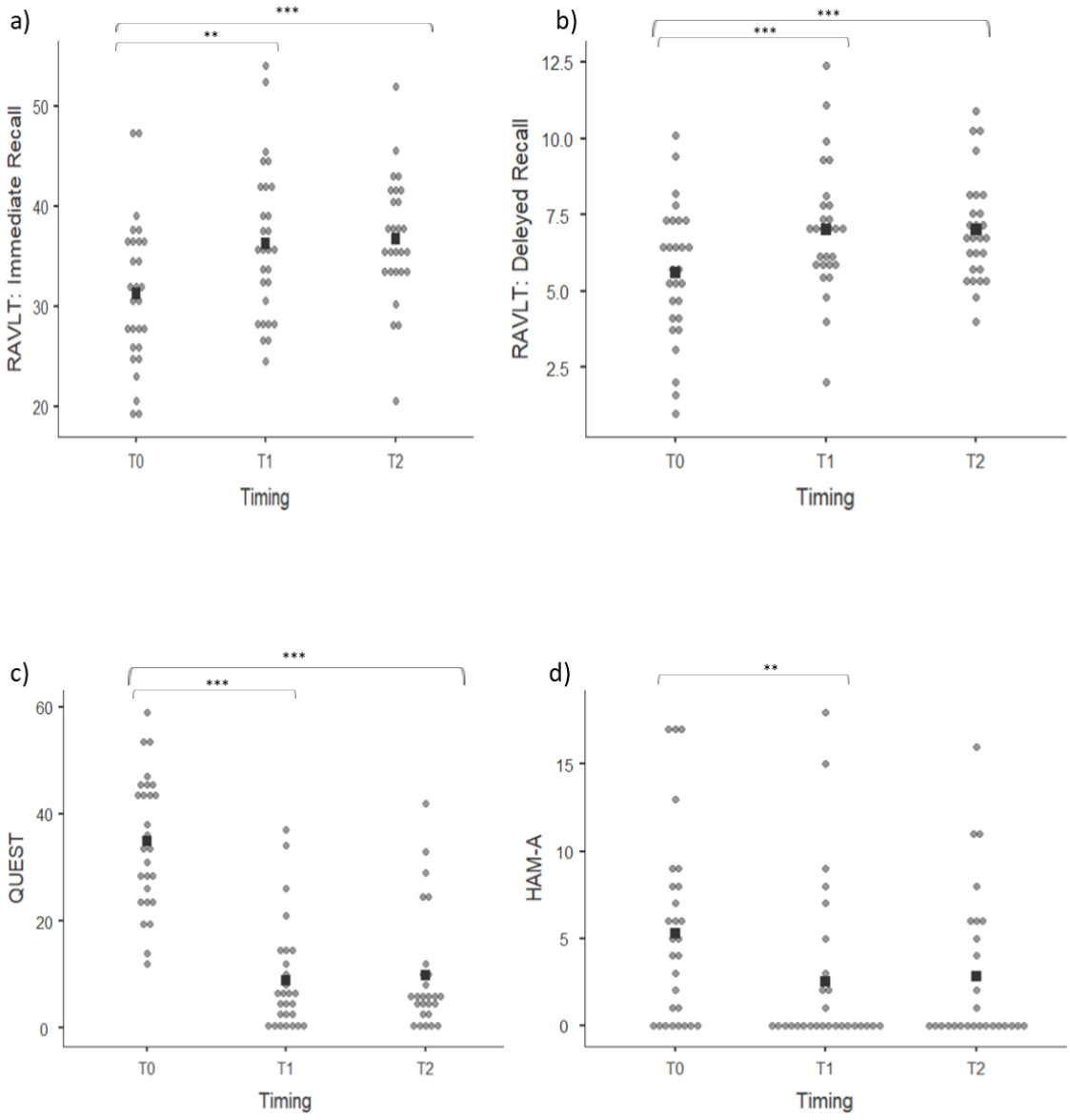

Figure 16 (a-d): Statistically significant changes in neuropsychological and neurobehavioral scores following the procedure in ET patients. Asterisks indicate significant p value (***< 0.001, **0.001).

	PD Patients					ET Patients				
Neuropsychological and Neurobehavioral tests	Baseline	6-months follow-up	1 Year follow-up	P-value 6 months	P-value 1 year	Baseline	6-month follow-up	1 Year follow-up	P-value 6-months	P-value 1 year
Mini Mental State Examination	26.64±2.71	28.13±1.99	28.09±1.98	0.014	0.022	27.95±1.96	28.42±1.46	28.52±1.42	0.186	0.063
Montreal Cognitive Assessment	22.64±4.30	23.27±4.05	23.41±3.78	0.162	0.081	23.89±5.39	24.18±3.27	24.30±3.53	0.777	0.737
Frontal Assessment Battery	14.18±3.03	14.73±2.62	14.82±3.10	0.194	0.294	14.29±3.10	15.64±2.13	15.44±2.44	0.004	0.023
Single letter-cued (phonemic) fluency test	28.56±10.55	28.84±13.30	30.10±11.48	0.881	0.316	26.31±9.17	27.91±7.59	27.83±7.87	0.199	0.164
Single letter-cued (semantic) fluency test	10.36±2.89	10.41±2.78	10.12±3.16	0.919	0.592	10.46±2.60	10.58±2.82	10.76±2.60	0.773	0.515
Rey Auditory Verbal Learning Test R.I	32.40±8.07	34.52±9.32	33.74±9.08	0.185	0.356	31.25±7.31	36.28±7.66	36.73±6.26	0.001	< 001
Rey Auditory Verbal Learning Test R.D	5.54±3.38	7.05±5.38	5.65±3.04	0.150	0.962	5.60±2.21	7.01±2.10	7.02±1.73	< 001	< 001
Raven's Progressive Matrices	28.39±4.84	28.00±6.23	28.29±6.33	0.278	0.808	28.87±4.71	29.63±4.05	29.35±3.95	0.127	0.520
Hamilton Anxiety rating scale	6.14±4.51	2.95±3.12	2.55±2.91	0.002	0.006	5.29±5.44	2.50±4.76	2.81±4.39	0.001	0.015
Beck Depression Inventory-II	4.73±3.30	2.86±3.23	1.68±2.46	0.081	0.003	2.96±4.04	1.14±1.96	1.89±3.07	0.023	0.112
Quality of life in Essential Tremor Questionnaire	-	-	-	-	-	35.00±12.08	8.93±9.86	9.03±10.64	< 001	< 001
Parkinson's disease Questionnaire-8 (PDQ-8)	8.10±2.97	3.11±1.56	3.10±2.34	< 001	< 001	-	-	-	-	-

Table 8 Change in neuropsychological and neurobehavioral scores between baseline, 6-months and 1 year follow-up for PD and ET patients.

When analyzing neuropsychological and neurobehavioral outcomes based on the treatment side, distinct patterns of improvement emerged, depending on whether the left or the right ventral intermediate nucleus (VIM) was targeted (Table 9). Specifically, following a left VIM thalamotomy, significant enhancements were observed in mnemonic functions [(RAVL: immediate recall 31.26 ± 7.40 vs. 35.09 ± 8.63; $p = 0.002$; RAVLT: delayed recall 5.31 ± 2.58 vs. 6.98 ± 4.06; $p < 0.001$), FAB 14.12 ± 3.01 vs. 15.21 ± 2.45; $p = 0.003$], as well as in quality of life (QUEST: 36.27 ± 11.80 vs. 9.88 ± 9.99; $p < 0.001$) and mood-related measures (PDQ-8: 7.47 ± 2.76 vs. 3.06 ± 1.53; $p < 0.001$; HAM-A: 6.02 ± 5.09 vs. 2.86 ± 4.36; $p < 0.001$) at both the six-month and the one-year follow-up visits [(RAVL: immediate recall 31.26 ± 7.40 vs. 34.89 ± 7.40; $p = 0.003$), BDI-II: 3.84 ± 3.79 vs. 1.71 ± 2.73; $p < 0.001$; HAM-A: 6.02 ± 5.09 vs. 2.74 ± 3.91; $p < 0.001$; QUEST: 36.27 ± 11.80 vs. 9.48 ± 11.07; $p < 0.001$; PDQ-8: 7.47 ± 2.76 vs. 3.11 ± 2.35; $p < 0.001$)].

Conversely, following a right VIM thalamotomy although improvements in quality of life and anxiety-depressive symptoms were noted, changes were not statistically significant (Table 9).

	LEFT VIM Thalamotomy					Right VIM Thalamotomy				
Neuropsychological and Neurobehavioral tests	Baseline	6-month follow-up	1 Year follow-up	p-value 6 months	p-value 1 year	Baseline	6-month follow-up	1 Year follow-up	p-value 6 months	P value 1 year
Mini Mental State Examination	27.34±2.42	28.45±1.51	28.33±1.68	0.004	0.010	27.54±2.35	27.31±2.51	28.31±1.86	0.750	0.293
Montreal Cognitive Assessment	23.40±4.99	23.77±3.77	23.95±3.41	0.080	0.008	23.00±4.96	23.85±5.27	23.57±5.09	0.457	0.174
Frontal Assessment Battery	14.12±3.02	15.21±2.45	15.05±2.87	0.003	0.032	15.00±3.31	15.42±1.98	15.85±1,77	0.824	0.548
Single letter-cued (phonemic) fluency test	27.25±9.93	28.24±10.64	28.95±10.00	0.381	0.077	27.61±9.42	28.81±9.36	28.24±7.51	0.725	0.835
Single letter-cued (semantic) fluency test	10.41±2.77	10.52±2.92	10.46±3.04	0.695	0.932	10.46±2.47	10.39±1.73	10.55±1.43	0.957	0.939
Rey Auditory Verbal Learning Test R.I	31.26±7.40	35.09±8.63	34.89±7.40	0.002	0.003	34.81±8.68	38.04±6.60	38.35±9.50	0.189	0.241
Rey Auditory Verbal Learning Test R.D	5.31±2.58	6.98±4.05	6.24±2.17	< 001	0.007	7.20±3.42	7.32±2.44	7.40±3.96	0.688	0.813
Raven's Progressive Matrices	28.69±4.24	29.41±3.98	29.10±3.97	0.074	0.427	28.45±7.44	25.81±9.54	27.50±10.01	0.059	0.611
Hamilton Anxiety rating scale	6.02±5.09	2.86±4.36	2.74±3.91	< 001	< 001	3.42±4.15	1.71±1.49	2.42±2.93	0.462	0.684
Beck Depression Inventory-II	3.84±3.79	1.84±2.81	1.71±2.73	0.004	< 001	3.14±4.10	2.28±2.05	2.28±2.30	0.833	0.684
Quality of life in Essential Tremor Questionnaire	36.27±11.80	9.88±9.99	9.48±11.07	< 001	< 001	24.00±10.00	1.66±0.57	5.00±4.58	0.250	0.250
Parkinson's disease Questionnaire-8 (PDQ-8)	7.47±2.76	3.06±1.53	3.11±2.35	< 001	< 001	9.50±4.35	3.35±1.70	3.00±2.30	0.125	0.098

Table 9 Change in neuropsychological and neurobehavioral scores between baseline, 6-months and 1 year follow-up finding by side (left/right).

When assessing correlations between motor tests and neuropsychological or neurobehavioral tests at one year after the treatment, a moderate negative correlation was found between the PDQ-8 score and the CRST total score (r= -0.467; p= 0.028), as well as between the CRST total score and FAB score (r= -0.408; p= 0.004). A strong negative correlation was found between the FAB score and the MDS-UPDRS-III score at 1 year (r= -0.745; p= < 0.001)

4.6 Discussion

As highlighted by a recent meta-analysis, the advantage of MRgFUS thalamotomy over other lesioning procedures might be due to the generation of smaller, more precise lesions, due to real-time monitoring of the lesion and thermographic feedback [20]. This enables operators to mitigate the majority of adverse effects by adjusting the initial target position during the procedure [21]. Neurological complications linked with MRgFUS VIM thalamotomy encompass reversible symptoms during the sonication phase, such as headache, dizziness, nausea, vomiting, sensations of heat or flushing in the scalp, paresthesias, and long-term symptoms like hypogeusia, gait disturbances, and, less frequently, unilateral weakness [22]. However, the majority of these complications are minor and typically resolve within a span of 3 months. These events can be classified as either MRI/ultrasound-related, arising from the procedural environment, or thalamotomy-related, triggered by the development of a lesion in the thalamus.

Despite some discomfort caused by the procedure, patients are confident in continuing a commitment to continue with the treatment [23]. Nonetheless, there is a minority of neurological complications that are challenging to be predicted and managed, such as gait disturbances, dysgeusia, incontinence, and cognitive changes.

The former are not easily identifiable as the patient is immobilized during the procedure: signs of cerebellar dysfunction can only be inferred by monitoring symptoms such as dysarthria and loss of coordination, which can be detected even with patient immobilization.

Consequently, signs of balance loss may manifest later, post-procedure, when the patient is able to of stand up and walk. Conversely, subtle cognitive disturbances are even more challenging to be detected unless the patient is assessed in the days and months following the procedure. Longitudinal follow-up assessments at predetermined intervals represent the sole dependable method to eliminate the possibility of lesion interference with normal cognitive function. Numerous studies have investigated alterations in cortical activity associated with MRgFUS thalamotomy [24,25]. Spectroscopy studies have suggested that MRgFUS therapy may facilitate the restructuring of neuronal networks and alter cortical activity, correlating with tremor improvement [24]. Furthermore, fMRI investigations have demonstrated that MRgFUS not only diminishes tremor symptoms but also reinstates the aberrant functional hierarchy in patients with ET [25].

Postmortem examinations have revealed the preservation of neurons within MRgFUS lesions in the VIM, indicating that the effects of VIM thalamotomy extend beyond coagulative necrosis to encompass the reorganization of extensive networks, including cerebello-striatal-thalamo-cortical pathways [26-28].

Thus far, the potential cognitive complications of VIM thalamotomy with MRgFUS have been relatively overlooked, likely due to the traditional perception of the VIM as solely a motor transmission hub.

As part of the lateral thalamic nuclei and integral to the "motor thalamus," the VIM serves as the primary nexus for cerebellar and pallidal projections to the cortex [21].

Both deep cerebellar nuclei (such as the dentate nucleus and interposed nuclei) and output nuclei of the basal ganglia (like the substantia nigra, reticulate portion, and globus pallidus, inner segment) project to the thalamus. Pallidal projections are predominantly situated in the anterior and medial regions of the VIM, whereas cerebellar connections are more prevalent in its lateral and posterior aspects [29]. Contrary to the conventional notion of a strict segregation between cerebellar and basal ganglia projections, recent hypotheses propose an interplay between these two systems [21]. Despite its primary involvement in motor functions, with cortical projections reaching primary, supplementary, premotor, and cingulate motor areas, the VIM likely contributes secondarily to cognitive functions as well, given its participation in the indirect pathway linking the prefrontal cortex to deep cerebellar nuclei [29].

The prefrontal cortex plays a pivotal role in various cognitive functions, often necessitating the synthesis and resolution of conflicting responses, integration of positive and negative information from diverse sources, and provision of contextually appropriate neural signals [30,31].

The connections between the cerebellum and cerebral cortex often exhibit bidirectional pathways, involving both the cortico-cerebellar pathway through the pontine nucleus and the cerebello-cortical pathway via the thalamus [31]. In contrast to ablative techniques, stimulation of the ventral intermediate nucleus (VIM) is more frequently associated with decreased word production speed and difficulty in switching between lexical fields, leading to a simplification of the syntactic structure used by patients. [32]

A recent study of bilateral deep brain stimulation (DBS) of the VIM showed a reduction in word production in both the active (ON) and inactive (OFF) conditions, with a more pronounced impairment in the ON state than in the OFF state [33]. This greater impairment in the ON condition was attributed to a perturbation of the thalamus, a key node in the regulation of flexible coupling of cortical areas during language tasks. Specifically, stimulation of the VIM can reduce network connectivity, decrease the spread of lexical activation, and slow down word production. [34]

This effect is related to a more anterior electrode position and greater amplitude of stimulation. However, the debate on the cognitive effects of DBS is still open and the results are controversial. Some studies found no significant cognitive changes following DBS of the subthalamic nucleus (STN) in either ON or OFF conditions. [35]

Another study found a comparable decrease in verbal fluency at three months compared with pre-surgical performance in both patients with active stimulation (ON) and an unstimulated control group (OFF). [36]

In this case, the decrease in verbal fluency performance can be interpreted as an effect of the implant itself rather than stimulation, suggesting a possible role of DBS electrode trajectory on post-surgical cognitive outcomes. A typical DBS electrode trajectory with a precoronal entry point traverses the prefrontal cortex, the subcortical white matter, the anterior margin of the internal capsule, and the basal ganglia, all structures involved in cognitive function. A recent study analyzed the relationship between electrode trajectories, their location and neuropsychological changes. [37]

The authors found that electrode trajectories that intersect with caudate nuclei increase the risk of a decline in global cognition and working memory performance, while a less precise orientation of active electrode contact within the STN is associated with a decline in verbal fluency. [38].

This suggests that, when possible, caudate nuclei should be spared from the electrode trajectory and that more antero-lateral paths are cognitively safer. [38]. In addition, precise orientation of the active electrode contact within the STN is essential to avoid subtle adverse effects on semantic verbal fluency after surgery.

Although mild cognitive complications have been observed following unilateral MRgFUS thalamotomy, such as specific cognitive impairments, overall cognitive safety has generally been observed [32,33].

Our COGNIFUS Part 1 study revealed no cognitive dysfunction at 6 months post-treatment, with improvements noted in anxiety levels and quality of life among MRgFUS-treated patients, without significant changes detected in individual cognitive domains.

The cognitive follow-up extended to 1 year in the COGNIFUS Part 2 study demonstrated advancements in specific cognitive domains and abilities, including enhancements in working memory, verbal memory, attention, and cognitive flexibility. This study marks a significant advancement in comprehending the non-motor consequences of unilateral thalamotomy with MRgFUS, suggesting its potential role in mitigating cognitive complications linked to dysfunctional neural networks. A conceivable explanation for the enhanced cognitive performance in treated patients is that the alleviation or disappearance of tremor may lead to overall improved well-being, thereby positively impacting their attentional state. Recently, an interpretative

phenomenological analysis-based study explored the experiences of ET patients undergoing treatment across the entire surgical process, from pre-surgery to post-surgery: all participants described tremor suppression as a pivotal life-changing event, with some individuals reporting a period of psychological adjustment to their altered bodily state. [32]

This highlights that tremor reduction exerts benefits beyond the motor domain and it can significantly influence patients' psychological welfare and cognitive functioning.

Conclusion

In summary, this doctoral research is focused on the potential cognitive function impairment in patients with PD and essential tremor ET, by investigating the non-motor impact of MRgFUS unilateral thalamotomy.

Indeed, MRgFUS is recognized as an emerging procedure for treating tremor and other neurological disorders, gaining popularity in clinical and research settings worldwide (39).

This research protocol took a significant step forward in identifying nonmotor outcomes of unilateral thalamotomy with MRgFUS, suggesting a potential role of the procedure in preventing cognitive complications mediated by maladaptive network formation. The most immediate hypothesis to explain the improvement in cognitive performance in treated patients is that the improvement or cessation of tremor may lead to greater well-being for patients, with positive effects on their attention status. Recently, a study based on interpretative phenomenological analysis explored the experiences of patients with essential tremor (ET) undergoing treatment throughout the entire surgical process, from the days before the procedure to the days after the procedure (34). After the procedure, all participants described tremor suppression as a life-changing event, with some expressing that they needed some time to adjust psychologically to what essentially became their new body (34).

This shows that tremor suppression has effects on patients that go beyond the motor dimension and can significantly affect psychological and cognitive spheres. An alternative hypothesis, which needs further confirmation from studies specifically designed for this purpose, is that thalamotomy may affect the functioning of subcortical networks that modulate the patient's cognition, particularly in terms of cognitive flexibility and attentional tone.

Strenghts of this research protocol include its prospective design, the longitudinal follow-up, and the stringent participant selection criteria, which excluded individuals with pre-existing cognitive impairments. Furthermore, the utilization of a comprehensive neuropsychological battery as compared to brief screening tools used in other investigations, strenghtes the reliability of the results. Another strength lies in the scheduled follow-up assessments at 6 months and 1 year post-treatment, which aids in mitigating potential biases stemming from learning effects in cognitive tests and allows for consistent monitoring of cognitive changes in Parkinson's patients, whose cognitive symptoms may evolve over time.

Nevertheless, a possibile limitation is the absence of validated tests for executive functions, such as the Stroop Color Test, the Trail Making Test (TMT), and the Wisconsin Card Sorting Test, within the neuropsychological battery. This test has been included in previous studies investigating the cognitive effects of DBS. We have not included this test so as to not extend the battery delivery time, which was already long enough.

Additionally, the study unveiled a predominance of males in the patient cohort, partly explained by the recognized gender disparity in PD.

However, this gender inconsistency has also been observed in individuals with essential tremor, indicating potential differences in access to treatment, influenced by various individual and social factors that deserve further investigation. Moreover, a relevant finding was the stronger association between left-sided VIM lesions and the observed enhancement in global cognitive performance, with concomitant reduction in anxiety levels. Nonetheless, caution is warranted in interpreting this outcome due to the limited representation of right-sided lesions in the sample. Future studies with larger cohorts are needed to thoroughly investigate the impact of lesion laterality on neuropsychological functioning and emotional well-being. Another aspect that will necessitate attention is the assessment of long-term cognitive safety subsequent to bilateral treatment. With the recent approval from the CE, patients will be eligible for contralateral treatment nine months post the initial intervention, provided they haven't experienced any adverse events. Throughout this PhD program, five patients, undergoing bilateral treatment underwent neuropsychological and behavioral assessments: at baseline, before th treatments, at six months and one year following the initial treatment, and at six months following the second treatment. Although preliminary, the analysis conducted allowed us to begin to delineate long-term safety even after bilateral thalamotomy.

However, to corroborate the long-term cognitive safety, it is essential to conduct longitudinal studies with a larger sample.

Appendix A

List of Pubblications:

1. Francesca Pistoia, Massimiliano Conson, Mario Quarantelli, Luca Panebianco, Antonio Carolei, Giuseppe Curcio, Simona Sacco, **Gennaro Saporito**, Ernesto Di Cesare, Antonio Barile, Carlo Masciocchi and Alessandra Splendiani. Neural Correlates of Facial Expression Recognition in Earthquake Witnesses. Front. Neurosci. 2019: Vol.13
2. Federico Bruno, Alessandra Splendiani, Emanuele Tommasino, Massimiliano Conson, Mario Quarantelli, **Gennaro Saporito**; Antonio Carolei, Simona Sacco, Ernesto Di Cesare, Antonio Barile, Carlo Masciocchi, Francesca Pistoia. Multimodal MRI Assessment of Thalamic Structural Changes in Earthquake Survivors. Diagnostics 2021; 11:70.
3. Francesca Pistoia, Agnes Shiel, Raffaele Ornello, **Gennaro Saporito**, Luca Gentili, Antonio Carolei, Carmine Marini, Simona Sacco; Franco Marinangeli. Translation and Transcultural Adaptation of the Wessex Head Injury Matrix, Italian Version: A Preliminary Report. Brain Sci. 2021;11;810.
4. Laura Sagliano; Massimiliano Conson, **Gennaro Saporito**, Antonio Carolei, Simona Sacco, Francesca Pistoia. Far from the mind: Preliminary evidence of avoidance bias for emotional facial expressions among earthquake victims. Elveiser. 2021;59;102273.

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6. Francesca Pistoia, Federico Salfi, **Gennaro Saporito**, Raffaele Ornello, Ilaria Frattale, Giulia D'Aurizio, Daniela Tempesta, Michele Ferrara, Simona Sacco. Behavioral and psychological factors in individuals with migraine without psychiatric comorbidities. J Headache Pain 2022; 23; 110.
7. **Gennaro Saporito**, Patrizia Sucapane, Raffaele Ornello, Davide Cerone, Federico Bruno, Alessandra Splendiani, Carlo Masciocchi, Alessandro Ricci, Carmine Marini, Simona Sacco, Francesca Pistoia. Cognitive outcomes after Focused Ultrasound thalamotomy for tremor: results from the COGNIFUS (COGNitive In Focused UltraSound) study. Parkinsonism & Related Disorders; 2022;106
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   Federico Bruno, Patrizia Sucapane, Carlo Masciocchi, Franco Marinangeli, Angelo Cacchio, Ernesto Di Cesare and Francesca Pistoia. Magnetic Resonance-guided Focused Ultrasound thalamotomy for refractory neuropathic pain: a systematic review and critical appraisal of current knowledge. Ther Adv Neurol Disord 2023, Vol. 16: 1–13.

9. **Gennaro Saporito**, Luca Gentili, Angelo Cacchio, Alfonsina Casalena, Stefano Necozione, Alessandro Ricci, Federica Venturoni, Franco Marinangeli, Francesca Pistoia. Assessment of frequency and predictive value of comorbidities in patients with disorders of consciousness in the acute setting. Neurotrama Reports. 2024**.**

10. Federico Bruno, Pierfrancesco Badini, Antonio Innocenzi, **Gennaro Saporito**, Alessia Catalucci, Patrizia Sucapane, Antonio Barile, Ernesto Di Cesare, Carmine Marini, Francesca Pistoia, Alessandra Splendiani. Early re-emerging tremor after MRgFUS thalamotomy: case–control analysis of procedural and imaging features. Front. in Neurol. 2024: 6:15:1356613

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12. Simone Cesarano, **Gennaro Saporito**, Patrizia Sucapane, Federico Bruno, Alessia Catalucci, Maria Letizia Pistoia, Alessandra Splendiani, Alessandro Ricci, Ernesto Di Cesare, Rocco Totaro and Francesca Pistoia. Staged magnetic resonance-guided focused ultrasound thalamotomy for the treatment of bilateral essential tremor and Parkinson's disease related tremor: a systematic review and critical appraisal of current knowledge. Front. in Neurol. 2024

13. **Gennaro Saporito**, Patrizia Sucapane, Federico Bruno, Alessia Catalucci, Carlo Masciocchi, Maria Letizia Pistoia, Alessandra Splendiani, Alessandro Ricci, Ernesto Di Cesare, Carmine Marini, Monica Mazza, Rocco Totaro, Francesca Pistoia. Cognitive safety of focused ultrasound thalamotomy for tremor: 1-year follow-up results of the COGNIFUS part 2 study. Front Neurol. 2024:17:15:1395282
14. Federica Guerra, Dina Di Giacomo, Jessica Ranieri, **Gennaro Saporito**, Patrizia Sucapane, Rocco Totaro and Francesca Pistoia. Network analysis of negative emotions in patients with episodic migraine: need for a multidisciplinary perspective". Frontiers in Neurology-Headache and Neurogenic Pain. 2024

List of abstracts:

1. Francesca Pistoia, Carmine Marini, **Gennaro Saporito**, Davide Cerone, Alessia Catalucci, Federico Bruno, Carlo Masciocchi, Simona Sacco, Tommasina Russo, Patrizia Sucapane, "Assessment of cognitive functions in patients undergoing Magnetic Resonance imaging-guided Focused Ultrasound (MRgFUS) ventral intermediate nucleus (Vim) thalamotomy", 51° Congresso Nazionale Società Italiana di Neurologia (Virtual Conference)

2. **Gennaro Saporito**, Giulia D'Aurizio, Francesca Pistoia, Raffaele Ornello, Valeria Caponnetto, Federico Bruno, Alessandra Splendiani, Simona Sacco, "Association between migraine and psychological and behavioural factors", The Internetional Headache Congress (Virtual Congress).

3. **Gennaro Saporito**, Patrizia Sucapane, Carmine Marini, Davide Cerone, Tommasina Russo, Simona Sacco, Francesca Pistoia, "Neuropsycological assessment in patients undergoing Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) thalamotomy. 7° Congresso dell'Accademia per lo Studio della Malattia di Parkinson e i Disordini del Movimento LIMPE-DISMOV.

4. Vincitore come miglior contributo scientifico in merito del 35° CONGRESSO NAZIONALE SISC - CEFALEE 2021: QUALI RISPOSTE ALLE NUOVE SFIDE: **Gennaro Saporito**, Giulia D'Aurizio, Francesca Pistoia, Raffaele Ornello, Valeria Caponnetto, Federico Bruno, Alessandra Splendiani, Simona Sacco. Association between behavioral factors and episodic or chronic migraine: A cross-sectional study. (Virtual Congress, 11-13 Novembre 2021)

5. **Gennaro Saporito**, Patrizia Sucapane, Carmine Marini, Davide Cerone, Tommasina Russo, Simona Sacco, Francesca Pistoia, "Neuropsycological assessment in patients undergoing Magnetic Resonance Imaging-guided Focused Ultrasound (MRgFUS) thalamotomy. 7° Congresso dell'Accademia per lo Studio della Malattia di Parkinson e i Disordini del Movimento LIMPE-DISMOV (Bologna 15-17 Dicembre 2021)
6. Relatore del Corso formativo "Congresso Regionale SINdem Abruzzo- PDTA Demenze: Sinergie tra ospedale e territorio per la presa in carico del paziente e dei suoi familiari". Palazzetto dei Nobili.
7. **Gennaro Saporito**, Patrizia Sucapane, Carmine Marini, Carlo Masciocchi, Alessandro Ricci, Davide Cerone, Tommasina Russo, Simona Sacco, Francesca Pistoia, "Assessment of cognitive outcomes in patients undergoing Magnetic Resonance Imaging-guided Focused Ultrasound thalamotomy (MRgFUS): long-term safety and efficacy". 8° Congresso dell'Accademia per lo Studio

della Malattia di Parkinson e i Disordini del Movimento LIMPE-DISMOV (16-18 Novembre 2022)

8. **Gennaro Saporito**, Patrizia Sucapane, Carmine Marini, Carlo Masciocchi, Alessandro Ricci, Davide Cerone, Tommasina Russo, Simona Sacco, Francesca Pistoia, "Assessment of cognitive outcomes in patients undergoing Magnetic Resonance Imaging-guided Focused Ultrasound thalamotomy (MRgFUS): long-term safety and efficacy". 8° Congresso dell'Accademia per lo Studio della Malattia di Parkinson e i Disordini del Movimento LIMPE-DISMOV (16-18 Novembre 2022)
9. **Gennaro Saporito**, Patrizia Sucapane, Carmine Marini, Davide Cerone, Tommasina Russo, Simona Sacco, Francesca Pistoia, "Gender differences in patients undergoing advanced therapies in Parkinson's disease (PD)", 52° Congresso della Società Italiana di Neurologia (SIN) (3-6 Dicembre 2022)
10. **Gennaro Saporito**, Patrizia Sucapane, Pio Crolla, Davide Cerone, Carmine Marini, Tommasina Russo, Francesca Pistoia; "Effects of gender difference in efficacy and adverse reactions to Safinamide.", 52° Congresso della Società Italiana di Neurologia (SIN) (Milano 3-6 Dicembre 2022)
11. Francesca Pistoia, C. Marini, **G. Saporito**, D. Cerone, T. Russo, P. Sucapane. Levodopa-carbidopa intestinal gel infusion associated complications: a retrospective study. 9° Congresso Nazionale della società italiana Parkinson e disordini del movimento LIMPE-DISMOV ETS (Padova 4-6 Maggio 2023).

12. Francesca Pistoia, S. Toro, F. Salfi, **G. Saporito**, G. Montaruli, M. Conson, C. Marini, M. Ferrara, P. Sucapane. Recognition of emotional faces and judgment of affective scenes in Parkinson's disease. 9° Congresso Nazionale della società italiana Parkinson e disordini del movimento LIMPE-DISMOV ETS (Padova 4-6 Maggio 2023).
13. Relatore nella tavola rotonda: "XXX GIORNATA MONDIALE DELL'ALZHEIMER: LA NUOVA FRONTIERA DEI TRATTAMENTI DI NEUROSTIMOLAZIONE TRANSCRANICA".
14. Patrizia Sucapane, **G. Saporito**, E. Di Sciullo, D. Murillo, V. Gazzotti, C. Marini, F. Pistoia. Transcranial pulse stimulation (TPS): a new method in the treatment of cognitive impairment. A preliminary study. XVII CONGRESSO SINDEM (Firenze 23-25 Novembre 2023
15. **Gennaro Saporito**, P. Sucapane ,F. Bruno , A. Catalucci, T. Russo, C Marini, D. Cerone , E Di Cesare , A. Splendiani, R. Totaro, F. Pistoia. High Intensity Focused Ultrasound (HIFU) treatment: evaluation of long-term cognitive outcomes. 10° Congresso della Società Italiana Parkinson e Disordini del Movimento/LIMPE-DISMOV ETS (Milano 10-12 Aprile 2024)

Papers under Rewiew

1) Giuseppe Maccarone, **Gennaro Saporito**, Patrizia Sucapane, Chiara Rizi, Federico Bruno, Alessia Catalucci, Maria Letizia Pistoia, Alessandra Splendiani, Alessandro Ricci, Ernesto Di Cesare, Marina Rizzo, Rocco Totaro and Francesca Pistoia. Gender disparity in access to advanced therapies for patients with Parkinson's disease: a retrospective real-word study. Frontiers in Neurology, Manuscript ID: 1429251
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Contribution to other research protocols

1) Voice Pattern analysis in Essential Tremor and Parkinson's Disease relater tremor.

2) Effectiveness and tolerability of rimegepant and lasmiditan as acute treatments: two prospective, multicentric, cohort studies.

3) Effects of transcranial pulse stimulation on functional and structural brain connectivity in Mild Cognitive Impairment and in the early stages of Alzheimer's disease.

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