Universitat de Girona
Facultat de Medicina

Repetitive Transcranial Magnetic Stimulation of Orbitofrontal Cortex for Empathy Enhancement in Behavioural Variant Frontotemporal Dementia

A randomized sham-controlled clinical trial to assess different intensities

- END OF TERM PROJECT -

Author: Júlia Thió Casals

Clinical tutor: Olga Belchí Guillamón

Methodologic tutor: Xavier Castells Cervelló

Hospital Universitari Josep Trueta, Departament de Neurologia, ICS
Unitat de Valoració de la Memòria i Demències (UVaMiD), IAS

Universitat de Girona – Faculty of Medicine

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ABSTRACT

Background

Dementias are the leading cause of disability in later life and, due the aging of the population, are predicted to increase its burden. Frontotemporal dementia is the second cause of early onset dementia, before Alzheimer's disease. Empathy loss is one of the core features of its behavioural variant, which impairs their social relationships and consequently reduces the quality of life of their familiars and caregivers. No therapy is approved for this dementia, and its management its mostly educational and symptomatic. Repetitive transcranial magnetic stimulation is a non-invasive, low-cost and available technique that is emerging as a potential therapeutic tool for multiple neurological and psychiatric conditions, showing potential to become a possibility to ameliorate social cognition deficits in these patients.

Objectives

The main purpose of this study is to test if repetitive transcranial magnetic stimulation, applied on the bilateral OFC in people suffering from behavioural variant frontotemporal dementia, could enhance empathy, comparing three different intensity parameters: sub-threshold, supra-threshold and sham stimulation. Secondary objectives include evaluating its effect on other cognitive areas and neuropsychiatric symptoms and improvement in caregivers quality of life; it will be assessed if atrophy degree interferes in the stimulation result and registered the tolerability and safety of the process.

Design and Methods

This study will be a randomized, single-blinded, multicentric, sham-controlled clinical trial. It will recruit 153 patients using a consecutive non-probabilistic method. Participants will be randomized in 3 arms following a 1:1:1 ratio; arm A) will receive subthreshold stimulation, arm B) suprathreshold stimulation and arm C) sham stimulation, for 4 consecutive weeks. Empathy will be assessed using Reading Mind in the Eyes test and Faux Pas test. Patients will be followed 1 year to assess therapy after-effects.

Key words: behavioural variant frontotemporal dementia; bvFTD; frontotemporal dementia; FTD; repetitive transcranial magnetic stimulation; rTMS; orbitofrontal cortex; treatment; empathy; theory of mind; ToM; reading mind in the eyes test; faux pas test

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1. ABBREVIATIONS

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
BNT	Boston Naming Test
bvFTD	Behavioural variant frontotemporal dementia
CBD	Corticobasal degeneration
CT-scan	Computed tomography scan
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
EEG	Electroencephalography
FAB-test	Frontal Assessment Battery test
FDA	Food and Drug Administration
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
FxP	Faux Pas test
GCA	Global cortical atrophy
hf-rTMS	High-frequency rTMS
IFCN	International Federation for Clinical Neurophysiology
IFG	Inferior Frontal Gyrus
IGT	Iowa Gambling task
IRI-E	Interpersonal Reactivity Index – Empathy
ITI	Inter-train interval
lf-rTMS	Low-frequency rTMS
LOCF	Last observation carried forward
lOFC	Lateral orbitofrontal cortex
LTD	Long-term depression
LTP	Long-term potentiation
MCI	Mild cognitive impairment
MEP	Motor-evoked potential
MMSE	Mini-mental State Examination

MRI	Magnetic resonance imaging
MT	Motor threshold
MTA	Medial Temporal lobe atrophy
NIBS	Non-invasive brain stimulation
nfvPPA	Non-fluent variant primary progressive aphasia
NPI	Neuropsychiatric inventory
OFC	Orbitofrontal cortex
PET	Positron emission tomography
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
RMET	Reading Mind in the Eyes test
rTMS	Repetitive transcranial magnetic stimulation
SPECT	Single photon emission computed tomography
STS	Superior temporal sulcus
svPPA	Semantic variant primary progressive aphasia
TBS	Theta-burst stimulation
tDCS	Transcranial direct current stimulation
TMT	Trail Making test
TMS	Transcranial magnetic stimulation
ToM	Theory of Mind
TPJ	Temporoparietal junction
vmPFC	Ventromedial prefrontal cortex
WHO	World Health Organization
ZBI	Zarit Burden Interview

2. INTRODUCTION

2.1. Background

2.1.1. Dementia and neurodegenerative diseases

Concept

Dementia is defined as an acquired syndrome consisting of a progressive global deterioration of intellectual functions, enough to cause disabilities or interfere in daily living activities, resulting in a diminished personal autonomy (1,2). That concept excludes syndromes presenting an altered level of awareness such as delirium, acute confusional syndrome (delirium) or coma; focal cognitive deterioration syndromes like isolated amnesia, aphasia or agnosia; either congenital syndromes (intellectual disability) (1).

It must be pointed out that the deterioration of the cognitive processes are required to interfere with social or occupational life to be considered dementia (3), thus excluding patients with a mild cognitive impairment (MCI) whom present some cognitive defects but are still capable of performing well in everyday life (1), and whom can or cannot evolve to a dementia (1).

Dementia is one of the major causes of disability in later life and it is the leading cause of dependency among older persons. It has a huge medical and psychological impact on those with the illness, families and, thus impairing their quality of life (4). It also threatens the sustainability of the public national health systems because it consumes lot of resources and it has an important economic burden (3).

Dementia: an emerging public health issue

At the beginnings of 1980s, dementia was considered a minor medical problem and it was attributed to aging processes or to arteriosclerosis (1). At that time, life expectancy at birth was only 62.9 years (5), and the population pyramid had a wide base shape. Nowadays, these concepts have enormously changed.

First, it has occurred an epidemiological change that modifies the age distribution. In Spain, life expectancy has grown from 75.5 years to 83.1 years, from 1975 to 2017, (6) and when combined with a decrease in the birth rate, that results in a rising of the proportion of people over 64 years (7) (see Figure 1). Therefore, the population age-distribution has evolved from a majority of young and mid-age people to an aged population (8) (see Figure 2).

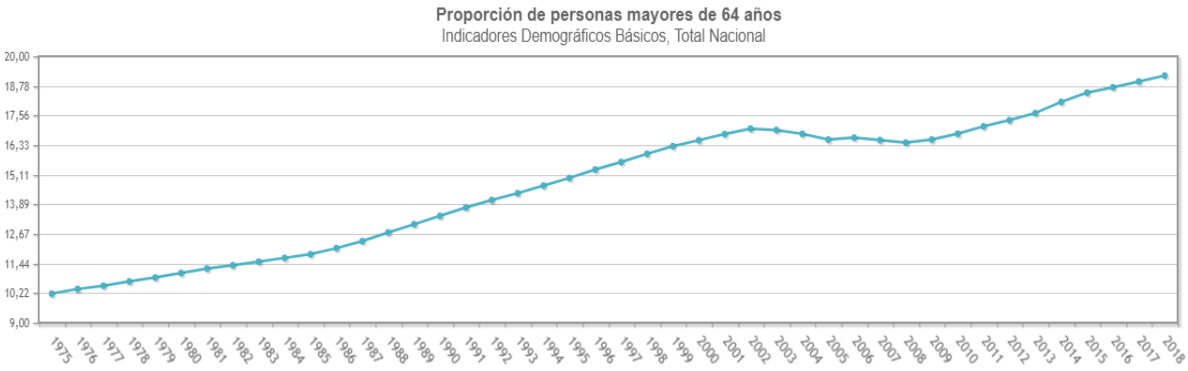


Figure 1. Proportion of people > 64 years in Spain, from 1975 to 2018. (From "Instituto Nacional de Estadística, INE").(7)

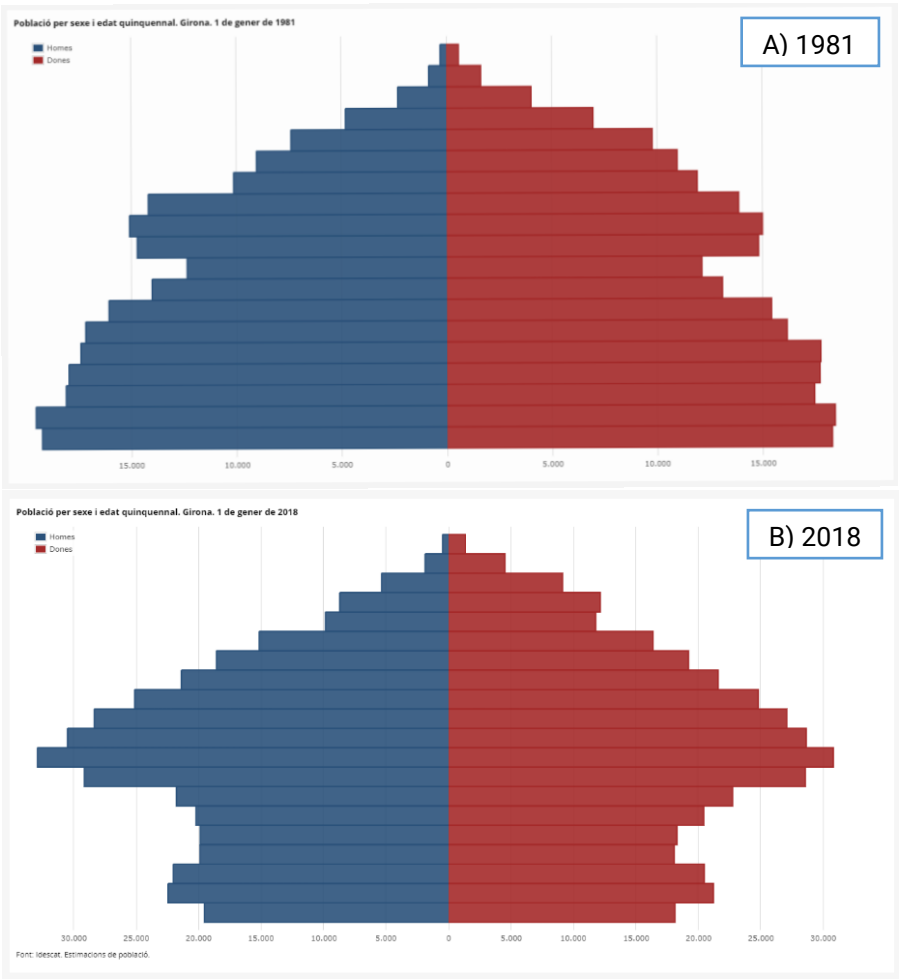


Figure 2. Differences in the population distribution for age (5 age-old clusters) and gender (males-blue, females-red), in the province of Girona between 1981 (A) and 2018 (B). (From IDESCAT, Institut d'Estadística de Catalunya) (8).

Secondly, dementia is no-more considered to be always necessarily liked to the aging process but understood as a heterogeneous pathological process that can be potentially treatable and in some cases preventable (1).

Epidemiology

Nowadays, dementia has an estimated prevalence of 6.5% among people > 64 years old and an estimated incidence between 10 and 15 new cases per 1000 persons-year (3). According to the World Health Organization (WHO), in 2017 around 50 million people suffered from dementia worldwide, and nearly 10 million new cases are registered every year.

Due to the rapid aging of the population (see Figure 3), dementia is projected to increase its burden (4,9,10) reaching a prevalence of 82 million in 2030, and 152 in 2050 (11). A major social and medical awareness also is contributing to increase dementia rates (3).

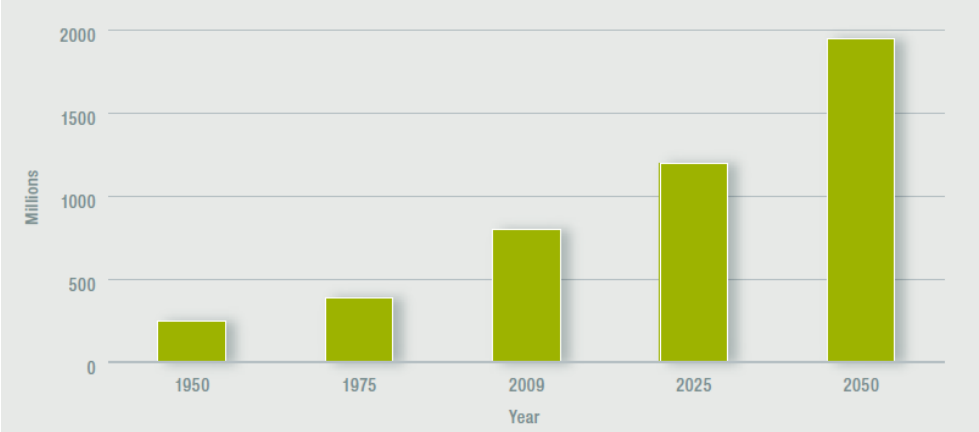


Figure 3. World population aged 60 years or over, 1950-2050. (From "Dementia: a public health priority") (4).

Alzheimer's disease (AD) is the most common form of dementia worldwide, representing the 60-70% of total causes of dementia, followed by vascular dementia (15-27%) and dementia associated to Parkinson disease (5-8%) (3). If it is taken in account also frontotemporal dementia (FTD), metabolopathies and normo-tensive hydrocephaly, they constitute the 95% of total dementia causes (1).

Risks factors

Aging is the most important risk factor to develop dementia (1,3). Other risk factors clearly associated to dementia are genetic factors (e.g. APOE ε4/ε4 for late onset AD), arterial hypertension, diabetes mellitus, a low educational level (related to low cognitive storage), smoking and presenting a MCI (3).

Other factors that may correlate to dementia but lack from consistent causality evidence are: hypercholesterolemia, adiposity, metabolic syndrome, major or chronic head trauma and nutritional factors (3). Instead, exercise and cognitive training may have a protective role (3).

Etiology

All the factors that damage the brain (neurodegenerative, toxic, metabolic, traumatic, infectious, tumoral or vascular) can potentially cause dementia (1).

The principal causes of dementia are the **neurodegenerative processes**, which are a wide group of diseases that progressively damage neurons (12). Neurodegenerative disorders share some common features: most of them have both sporadic and inherited origins, usually they appear later in life and their pathology is characterized by neuronal loss and synaptic abnormalities caused by misfolding aggregation and accumulation of proteins in the brain (13). Although these similitudes, the clinical expression of the neurodegenerative conditions differ depending on the area of nervous system they affect (3) and on the type of proteins it is accumulated (13).

Diagnosis

Dementia diagnosis is supported by clinical history, physical exploration, neurological examination, neuropsychological testing and neuroimaging (CT-scan, MRI, PET or SPECT) (1). It is important to perform blood analysis to discard treatable causes of cognitive deterioration (e.g. metabolic causes). In selected patients we can rule out an electroencephalography (EEG) or lumbar puncture; when are suspected some specific pathologies (3).

2.1.2. Behavioural variant frontotemporal dementia (bvFTD)

Concept

Frontotemporal dementia (FTD) is a type of dementia that, as its name reveals, progressively affects the frontal and/or the temporal lobes (2). This brain regions are implicated in motivation, reward processing, personality, social cognition, attention, executive functioning and language (14). Therefore, FTD insidiously impairs behaviour, language and/or executive functions (1,15).

FTD is not a disease itself, but rather a wide heterogenous group of syndromes that differ in etiology, anatomopathological features, genetics, clinical onset and brain atrophy patterns (15). Some authors prefer the term frontotemporal lobar degeneration (FTLD) instead of FTD (2,3,16), but this name can lead to misunderstandings, as is an anatomopathological concept expressing the brain atrophy seen in these conditions. Clinically, FTLD can be associated to cognitive syndromes, like FTD; and non-cognitive syndromes, such as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) (16,17). The term FTLD will be reserved for patients

with clinical presentation of FTD with an identified FTD-causing mutation or histopathologic evidence (17).

Epidemiology

FTD is considered the third most common form of primary dementia (i.e. without recognizable underlying cause), after AD and Lewy bodies dementia (2,18) and it represents the second most common cause of early onset dementia (i.e. dementia starting under 65 years of age) (15,17). In some studies, it is reported to equal AD prevalence and incidence in < 60 years-old people (16).

FTD typically develops on the sixth decade of life (19), but it can extend from 40 to 80 years of age (16). The highest prevalence occurs in the 45-64 years of age group (see Figure 4), accounting for 60% of FTD. In this age range, FTD has an estimated prevalence of 15-22/100,000 people and an estimated incidence of 2.7-4.1/100,000 person-years (16). Only 10% of cases occur in < 45 year-old and approximately 30% in ≥ 65 years of age (16). FTD affects both genders equally in a rough 1:1 proportion (17,19).

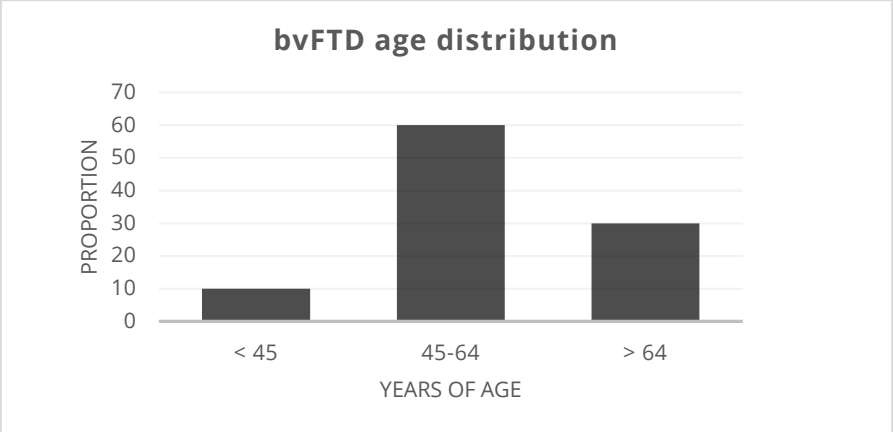


Figure 4. Proportion of bvFTD among age groups. Data from Knopman et al. 2011 (16).

The passive surveillance system of dementias in the sanitary region of Girona (ReDeGi) documented 241 new cases of dementia related to FTD, between year 2007 and 2017, representing 2.97% of total registered cases (Figure 5).

Types of FTD

FTD is subdivided in three main clinical categories: 1) **behavioural** variant FTD (bvFTD, sometimes also called frontal variant), 2) **non-fluent** variant primary progressive aphasia (nfvPPA), presenting with progressive deficits in motor-speech, grammar and word output; and 3) **semantic**

variant primary progressive aphasia (svPPA), associated to insidious semantic and naming impairment (14,17,18).

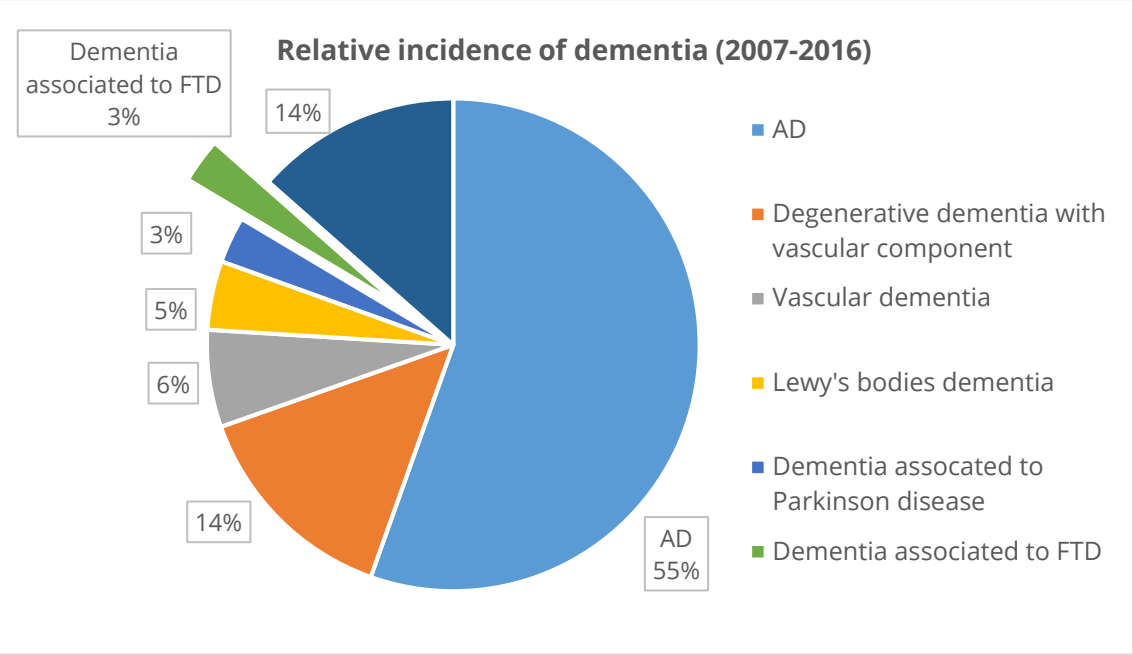


Figure 5. Relative incidence of types of dementia between 2007 and 2016 in the sanitary region of Girona. Data used from "Registre de Demències de Girona, Memòria 2017" (20).

BvFTD is the most common form of the three main clinical subtypes of FTD, representing approximately 60% of FTD cases (16,19) and it is characterized by an early impairment of social cognition, personality and executive functions (3,18).

The last two subtypes are part of primary progressive aphasia (PPA) (14), which is a syndrome –not a pathological diagnosis –, consisting of impairment in expressive and/or receptive language functions (2). Apart from nfvPPA and svPPA it exists a third subtype called logopenic variant (lvPPA) which is not included into the FTD's spectrum and it is more related to AD (2).

The three major FTD categories not only differ in clinical presentation, but also have discrepancies in brain lesions patterns and disease course (14). Over time, FTD subtypes converge and patients develop a global dementia that can also show motor neuron deficits (18).

Risk Factors and Neuropathology

Approximately 50-60% of FTD is considered to be sporadic, and the other 40% accounts for familial cases (17).

There are few studies evaluating **environmental risk factors** of FTD and they only identified a link between repetitive head concussions and cognitive deficits and pathologic tau deposition (17).

Regarding **genetic** cases, 94% are inherited in an autosomic dominant pattern and the remaining ones are considered sporadic mutations (17).

Eight genes are responsible for approximately 50% of familial FTD, described on Annex 1. Mutations in *progranulin* (**GRN**), *chromosome 9 open reading frame 72* (**C9ORF72**) and *microtubule-associated protein tau* (**MAPT**) genes are responsible for most of cases (17).

When looking in brain tissue, most of the anatomopathological accumulations of proteins are **tau** or **TDP-43** inclusions, and the remaining 10% contain FUS protein (2).

Signs and symptoms

The main feature of bvFTD is the **behavioural impairment** manifested in a variety of forms that can include personality change and altered social cognition (2). It also can present deficits in executive functions and/or psychotic symptoms (15,17).

BvFTD patients usually become **disinhibited**, manifesting increased disclosure of personal information, impulsivity, inappropriate social behaviour, loss of manners, increased sexual interest or usage of offensive language (2,15,17). Some can present with poor grooming and lack of **hygiene** (2,17). They also may show **loss of empathy** or sympathy, becoming unaware to the feelings and thoughts of the others (2,15,17).

Other common early features are abulia and **apathy**, displayed as lack of motivation and reduced of interests, although they can show childly o restless affect (2,15,17). Frontal lobe deficits might produce **repetitive/perseverative** behaviours (15,17) such as counting, touching items of the room, having ritual behaviours and using stereotyped speech. BvFTD patients can also present with **utilization** and **imitation** behaviour, and may develop **hyperorality** (15,17) and dietary changes, with increased food or inedible objects consumption, drug abuse behaviours or altered food preferences.

Few studies reported **impaired language** (2), describing it as echolalia, reduced spontaneous speech or muteness and stereotyped sentences; rather than aphasia itself, so it is considered a consequence of the apathetic and perseverative mood, preserving the language abilities intact. BvFTD may also present **psychotic** symptoms including visual or auditory hallucinations or delusions (17), although it is not its classical clinical feature.

Diagnosis

The diagnosis of bvFTD is challenging; the younger age distribution compared to other dementias, the possible similitude to psychiatric conditions, the wide range of presentations and the low disease prevalence all contribute to make diagnosis of bvFTD into a tricky task (18). Therefore, it is assumed that there is a lack of recognition of FTD and that the prevalence is likely underestimated (14,15).

Due the lack of validated neurologic biomarkers and useful blood analysis tests, the diagnosis process is mostly clinical (2). It is supported by clinical evaluation, neurological assessment and neuroimaging; which help to identify syndrome's core features (21), (Figure 6).

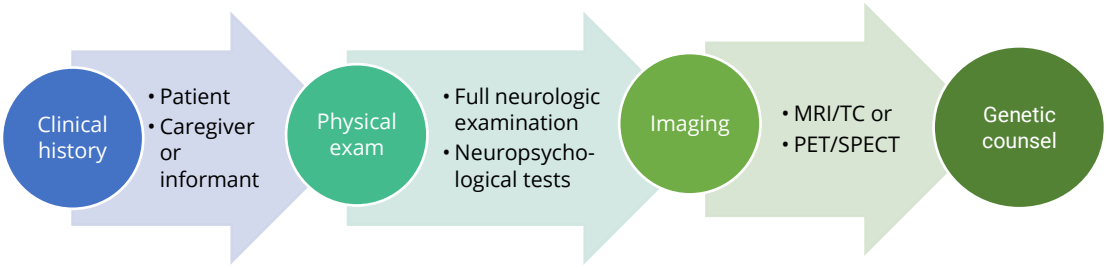


Figure 6. FTD diagnostic process

On 2011, the International Behavioural Variant FTD Criteria Consortium (FTDC) developed a revised guidelines for the diagnosis of bvFTD (see Annex 2) (21). According to these criteria, "**possible**" bvFTD requires three of six discriminating features (disinhibition, apathy/inertia, loss of sympathy/ empathy, perseverative compulsive behaviours, hyperorality and dysexecutive neuro-psychological profile). "**Probable**" bvFTD adds functional disability and characteristic neuroimaging (frontal and/or anterior temporal atrophy or hypometabolism), and "**definitive**" bvFTD meets "possible bvFTD" criteria and histopathological evidence and/or a known pathogenic mutation. See Table 1 for a summary of the criteria.

Table 1. Types of bvFTD according to International Criteria Consortium, from Rascovsky et al. 2011 (21).

Type of bvFTD	CRITERIA
Possible bvFTD	**3 out of 6** from the following **symptoms**: - disinhibition - apathy/inertia - loss of sympathy/ empathy - perseverative compulsive behaviours - hyperorality - dysexecutive neuropsychological profile
Probable bvFTD	Possible bvFTD + functional **disability** + compatible **neuroimaging**
Definitive bvFTD	Possible bvFTD + **neuropathological** evidence or pathogenic mutation

Personal history and neurologic examination

BvFTD diagnosis requires a complete and exhaustive history with the patient and the caregiver or informant. BvFTD patients usually have little insight, and it is necessary to count on a reliable source to identify the baseline personality traits and habits, and then assess the relative change form start point (17). It is important to consider actual life events and relationship factors that can explain or modify the behaviour (17). On the physical examination it can be found grasping, snout reflex and others signs of frontal release (17).

Neuropsychological tests

Early bvFTD patients typically demonstrate impaired executive function tasks (15), with relative preservation of memory and visuospatial domains, contrary to AD. Later, all domains can be affected, as it evolves to a global dementia (22).

Cerebrospinal fluid (CSF) and serum biomarkers

At present, no validated biomarkers exist (17). Amyloid-β_{42} and tau in CSF are under investigation and in the future may be able to distinguish AD and FTD. Low progranulin levels in serum could be able to predict GRN mutations, but it is still far from practical clinical use (17).

Neuroimaging

The hallmark finding in bvFTD is the **frontal** or **anterior temporal** lobe atrophy on MRI or CT-scan. Studies report different atrophy patterns according to the mutated gene and the type of FTD; PPA variants show more atrophy on the areas associated to expressive speech and syntax (2,14,15).

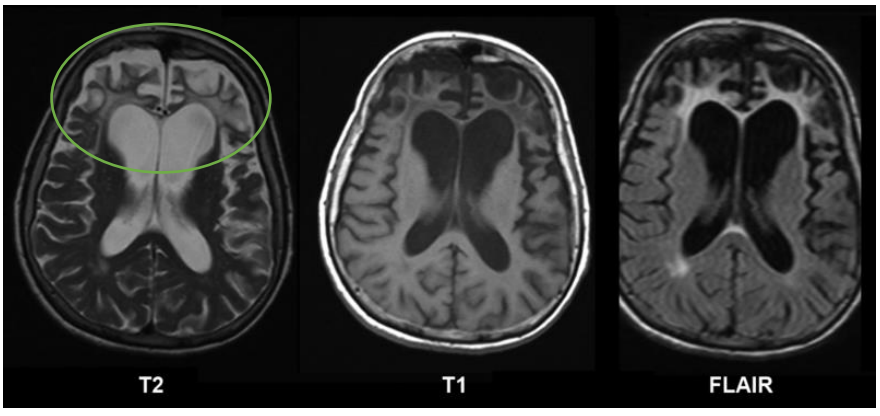


Figure 7. Bifrontal lobe atrophy seen on MRI. Modified from "Viquipèdia - Pick's disease" (free-license image) (23).

Nuclear imaging can be very helpful in differentiating AD from FTD. SPECT shows patterns of hypoperfusion that can distinguishing FTD from AD with 80% of sensitivity. Fluorodeoxyglucose

positron emission tomography (FDG-PET) has a 90% of accuracy, and usually FTD presents a hypometabolism on the right temporal lobe or right/bilateral frontal lobe. Another new PET scan that detects the level of amyloid (PET-amyloid) also can help differentiating AD and FTD, with 90% of accuracy (17).

Genetic counselling

Patients with positive family history or who are interested in genetic testing can perform genetic counselling to assess their genetic status and the chances to transmit the illness (17).

Treatment

There are currently no therapies specifically approved for FTD able to cure or modify the natural history of the disease (17). Therefore, its management consists on family and patient education and support and little symptomatic pharmacologic treatment.

Supportive management and follow-up assessment

Assessment on how to manage finances, driving and personal care is really important because impulsivity and impaired judgment that bvFTD patients present can result in economic difficulties and increased rate of car accidents. Caregivers should be referred to dementia support groups for emotional accompaniment and education of strategies to manage bvFTD behaviours (17), as they suffer a lot of stress due the social impairment of this patients (24).

Symptomatic treatment

The aim of pharmacological treatment, used off-label, is to modify difficult behaviours and other psychiatric symptoms (17). The most common used medications are **selective serotonin reuptake inhibitors** to manage disinhibition, agitation, irritability and compulsions; and **neuroleptics** for psychosis and aggressive behaviour. If the patient shows parkinsonism, **carbidopa or levodopa** can be trialled, although clinical response is infrequent (17). No current medication is used to treat apathy, loss of empathy or executive dysfunction.

Prognosis

FTD patients have a bad prognosis. The mean survival time is about 7-10 years after symptoms onset and only 3-4 years from the time of diagnosis due the large delay on diagnosis (16). Death is typically caused by pneumonia or other infections or complication of falls (17,18).

2.1.3. Neuropsychological concepts of empathy

What is empathy?

Empathy can be broadly defined as individual's ability to understand and feel the other's emotional states (25,26). Empathy is critical for appropriate and effective social interaction and comprehension, but is not enough (26). The understanding of other's beliefs and emotions does not guarantee feeling them, neither empathy guarantees an appropriate social response such as manifesting sympathy, care or support (26).

Empathy is broken down into two different systems (see Table 2. Two different systems of empathy and its function.): (a) cognitive empathy, "mentalizing" or theory of mind (ToM) and (b) affective or emotional empathy. The first one refers to the ability to attribute mental states to the others, whether being thoughts and beliefs (cognitive ToM) or emotions (affective ToM). ToM allows you to understand, predict and anticipate others' behaviours. Instead, affective empathy consists on adopting other's feelings as yours; it is not about *thinking* but *feeling* (26). All these capacities are needed when talking about social cognition.

Social cognition is related to **interpersonal functioning**; numerous conditions performing worst ToM and affective empathy tests (e.g. autism, schizophrenia), present with significant social interaction deficits (27). Therefore, improving social cognition may improve social performance.

Table 2. Two different systems of empathy and its function.

	SYSTEM		ABILITY
	Cognitive empathy	Cognitive ToM	*"I **know** what the man is **thinking**" (i.e. thinking about the accident)*
		Affective ToM	*"I **know** what the man is **feeling**" (i.e. feeling desperate)*
	Affective empathy		*"I **feel** the way the man is **feeling**" (i.e. I feel his desperation)*

Neuroanatomical networks

Empathy networks have been elucidated through neuroimaging functional studies, patients with brain injuries or neuropsychiatric conditions, and developmental disabilities (e.g. autism) (26).

The three different empathy systems relate to different brain networks (Figure 8). Cognitive ToM has been mostly linked to **dorsolateral prefrontal cortex** (DLPFC), but other important structures are dorsomedial prefrontal cortex (dmPFC), temporoparietal junction (TPJ), superior temporal sulcus (STS), dorsal anterior cingulate cortex (dACC) and temporal pole (TP). Affective ToM is more related to **orbitofrontal cortex** (OFC), which is divided into ventromedial prefrontal cortex (vmPFC) and lateral OFC (lOFC); and to inferior frontal gyrus (IFG). Affective empathy, instead, is dependent of the anterior cingulate cortex (ACC), IFG and **amygdala** (26).

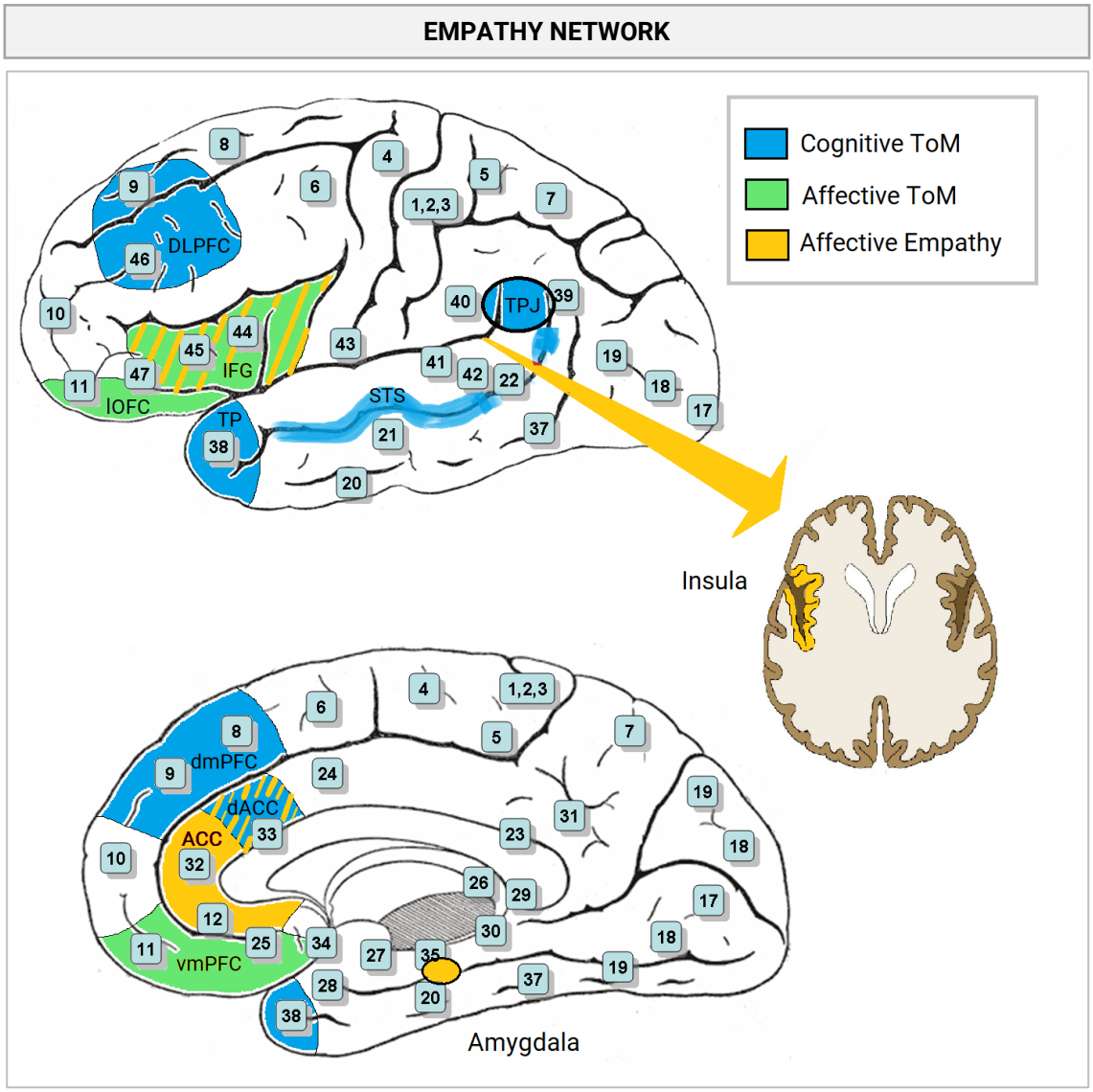


Figure 8. Neuroanatomical areas associated with empathy. Different colours represent different empathy systems: blue – cognitive ToM, green – affective ToM, orange – affective empathy //ACC: anterior cingulate cortex; dACC: dorsal ACC; DLPFC: dorsolateral prefrontal cortex; dmPFC; dorsomedial prefrontal cortex; IFG: inferior frontal gyrus; lOFC: lateral OFC; STS: superior temporal sulcus; TP: temporal pole; TPJ: tempoparietal junction; vmPFC: ventromedial prefrontal cortex. Brain baseline picture from "Anatomy of the human body" (28)*, free-license images.*

The main difference between cognitive and affective empathy is the participation of amygdala; which belongs to the limbic system and therefore is fundamental for the *feeling* capacity. The vmPFC has connections with the amygdala and other limbic structures, thus explaining why is relevant in affective ToM: vmPFC links emotional and cognitive processes (29).

Empathy is based on a complex interrelated network and is not mapped in a single brain area.

bvFTD and social cognition

Socioemotional disturbances, including emotional blunting and social disinhibition are considered one of the core features of bvFTD according to the recent international consensus criteria (21). Empathy impairment in these patients is not surprising, as this dementia causes atrophy in brain regions that have a primary role in social cognition such as vmPFC, lOFC and frontoinsular cortices (27).

Recently, numerous studies have examined ToM and affective empathy on AD and bvFTD. On 2015, a meta-analysis comparing ToM performance in bvFTD and AD (27) found that bvFTD tests were significantly more impaired when compared to healthy controls and AD patients. Another meta-analysis published on June 2018, assessing affective empathy in bvFTD (25), found that these patients performed at a reduced level on emotional empathy tasks when compared to other populations. Most of the studies included in this meta-analysis used the empathy concern subscale of the Interpersonal Reactivity Index (IRI-E), assessed by caregivers, indicating that caregivers feel a lack of warmth and connectedness to bvFTD relatives (25).

These results suggest that empathy tests could be used to differentiate the early stages of AD and bvFTD (25,27,30). Even though, most of these studies have small sample sizes and present significant methodological variability, highlighting the necessity of larger controlled clinical trials to confirm this hypothesis.

Measures of empathy

As explained, empathy is a multidimensional and complex function and therefore its neuropsychological assessment is complex either. Lots of tests have been developed to assess alterations in empathy, and every test correlates to a different system of empathy (cognitive or affective) and to a certain brain network (29). Despite this fact, on this section there will be discussed only the ones used in this study: the "**Reading mind in the eyes test**" (RMET) and "**Faux Pas test**" (FxP).

Even though these tests are not validated in FTD (no validated empathy tests exists), RMET and FxP have been used before in bvFTD and they seem to be the ones that are more impaired when performed also by AD (27,30) and healthy age-matched adults (31), even in early stages of dementia, comparing to other empathy tests. These tests are available, easy to apply and can be delivered in short-time.

Reading Mind in the Eyes Test

The revised version of RMET test – Baron-Cohen *et al.* (2001) (32) (Annex 3) –, initially elaborated to assess affective ToM in Asperger's syndrome and high-functioning autism (33), consists of 36 grey-scale photos which show the ocular region of a person, whom eyes express a feeling. Each photo is surrounded by four possible mental states and the subject has to choose and mark word that better describes the photo (29) (Figure 9). To correctly perform RMET, the subjects need to identify the emotion, be able to complete the facial expression and understand the mental state meaning (29), thus principally assesses cognitive ToM function. To avoid vocabulary limitations, the test provides a definition hand out that can be checked anytime.

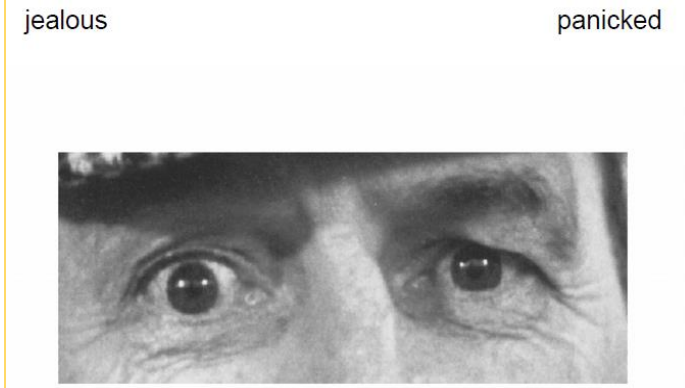
The test includes both basic (e.g. sad, happy, angry) and complex (e.g. arrogant, reflective) mental states (33), involving different neuroanatomical regions according to the complexity of feeling. Amygdala takes part in basic emotions recognition and frontal and temporal lobes are related to more complex states (29); reflecting that RMET could also be an affective empathy test. This dual component is one of the main reasons that RMET was chosen for this study.

Jealous

Envious
*Tony was **jealous** of all the taller, better-looking boys in his class*

Arrogant

Conceited, self-important, having a big opinion of oneself
*The **arrogant** man thought he knew more about politics than everyone else in the room*



Panicked

Distraught, feeling of terror or anxiety
*On waking to find the house on fire, the whole family was **panicked**.*

Hateful

Showing intense dislike
*The two sisters were **hateful** to each other and always fighting.*

Figure 9. Example photo of RMET revised version and the definition of the mental states (Baron-Cohen, 2001)[1].

[1] From http://www.autismresearchcentre.com/arc_tests.

Faux Pas Test

FxP – Stone *et al.* (1997) and Gregory *et al.* (2001) (30,34) – consists of 20 stories: 10 of them contain a social *faux pas* and in the other 10, used as controls, the *faux pas* is not committed (29). The patient must read the story and after that some questions are made, (see Figure 10 for an example of a FxP story).

First, it is assessed if the subject is able to identify a social *faux pas*, asking him/her to tell if anyone said something inappropriate and who was. If it is identified, then some clarifying questions are made: "Why shouldn't they have said it?" and "Why do you think they said that?". They assess if the subject understood the inappropriateness and if he/she is aware that the *faux pas* was committed unintentionally. After that is asked "How did X feel about the *faux pas*?" in order to evaluate the ability to imagine the feelings of the character that was accidently hurt. Finally, two control memory questions are used to check the attention and the global understanding of the story.

In order to comprehend that a *faux pas* has occurred, the subject has to represent two mental states: (A) that the person who committed a *faux pas* is unaware that said something inappropriate and (B) that the person hearing might feel upset, hurt or insulted (30). For that reason, FxP assesses both types of ToM: cognitive and emotional. When taking in account the neuroanatomical region related to FxP, vmPFC was the most correlated area (29).

Story 2. Helen's husband was throwing a surprise party for her birthday. He invited Sarah, a friend of Helen's, and said, "Don't tell anyone, especially Helen." The day before the party, Helen was over at Sarah's and Sarah spilled some coffee on a new dress that was hanging over her chair. "Oh!" said Sarah, "I was going to wear this to your party!" "What party?" said Helen. "Come on," said Sarah, "Let's go see if we can get the stain out."

- Did anyone say something they shouldn't have said or something awkward?

If yes, ask:

- Who said something they shouldn't have said or something awkward?
- Why shouldn't he/she have said it or why was it awkward?
- Why do you think he/she said it?
- Did Sarah remember that the party was a surprise party?
- How do you think Helen felt?

Control questions:

- In the story, who was the surprise party for?
- What got spilled on the dress?

Figure 10. Story number 2 of the adult English version[1] of the FxP corresponding to a faux pas story, from Stone et al. (1998) and Gregory et al. (2002).

2.1.4. Repetitive Transcranial Magnetic Stimulation (rTMS)

Basic concepts

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation and neuro-modulation technique that delivers magnetic pulses to the brain capable of depolarizing neurons and modulate cortical excitability (35,36). TMS, together with transcranial direct current stimulation (tDCS), are considered the non-invasive brain stimulation techniques (NIBS) (37). NIBS initially were developed as tools to study brain function, but they are emerging as potential therapies for multiple neurologic and psychiatric syndromes (37,38).

Neurophysiological concepts: Interaction of the magnetic field with brain tissue

To generate a single TMS pulse, an electric current is passed through a coil generating a magnetic field perpendicular to the plane of the coil (38) (Figure 11). This magnetic field penetrates scalp and skull and induces an electric field in the underlying brain tissue (35), which generates an ion flow that modifies the electric charges of the neurons' cell membranes, producing its depolarizing or hyperpolarizing (35).

The effect of TMS is variable depending on the individuals condition. It can be altered for changes in the anatomy of brain (atrophy, tumor, stroke) which modify conductivities and resistance of the tissue (35). In addition, numerous studies point out that TMS-effectiveness strongly depends on the neuronal activation status in the targeted brain region at the time of stimulation (35). Menstrual cycle, level of anxiety or mood, sleep deprivation, occult substance abuse and other factors modulate the effect of TMS (35).

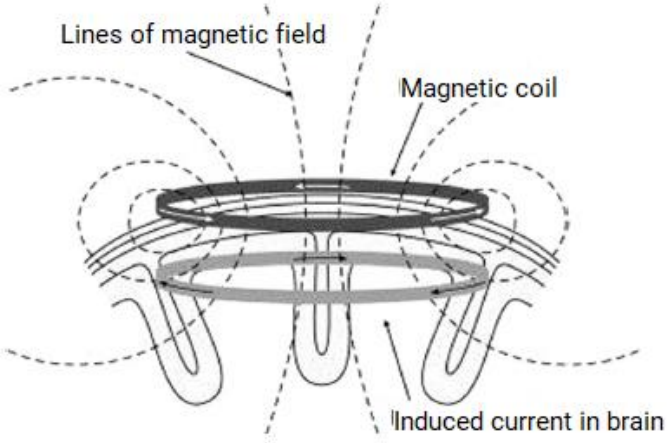


Figure 11. Direction of current flow in a magnetic coil and induced current in the brain. Modified from Rossini et al. "Non-invasive electrical and magnetic stimulation of the brain…" 2015 (39).

Types of TMS and rTMS induced responses

According to the number of stimulus applied at a time, TMS can be classified into: (A) *single pulse TMS*, (B) *paired-pulse TMS* and (C) *repetitive TMS* (rTMS) (35). Single-pulse TMS enables to study cortical reactivity by mapping motor cortical outputs and central motor conduction time. Paired-pulse technique can assess functional integrity of intracortical facilitation and inhibition circuits (35,38). Instead, when TMS is applied repetitively, it can induce changes in brain activity that can last beyond stimulation period (38,40). Consequently, single and paired-pulse TMS are used for diagnosis purposes and rTMS for therapeutic ones.

The physiological mechanisms of rTMS aftereffects are still not clarified, but seems that they resemble **long-term potentiation** (LTP) and **long-term depression** (LTD) processes (40). LTP and LTD traduce long lasting changes in synaptic unions, related to activation or inhibition of NMDA and AMPA receptors, that turn neurons into more or less sensitive to synaptic signalling (40). Other complex mechanisms different from LTP and LTD have also been related to the neurophysiologic substrate of rTMS aftereffects (35).

Parameters in rTMS stimulation protocols

The length of the stimulation period, the intensity, ITI, the total number of pulses and the type of coil are parameters that modify the type and duration of the aftereffects (40), and are relevant in security terms. Then, to decide the "dose" of stimulation, all the following parameters must be taken in account:

- Intensity: expressed as % of motor threshold (MT).

  MT reflects the excitability of the cortex (40) and is determined using single-pulse TMS. When the coil is placed over the motor cortex (M1 or central sulcus) the pyramidal neurons are depolarized, propagating the stimulus along the corticospinal pathway and eliciting a motor-evoked potential (MEP). MEP amplitude and latency can be recorded using a surface electrode positioned on the contralateral muscle of interest (i.e. abductor pollicis brevis) (38). MT is defined as the minimum TMS intensity of motor cortex stimulation required to evoke MEP of a determined amplitude in about 50% of 5-10 consecutive trials (39,40). The amplitude is 50μV at rest – resting MT – and 200μV during 20% of maximum contraction – active MT –. An intensity below 100% of MT its named **sub-threshold** and above MT is considered **suprathreshold** stimulation.

- Frequency. Number of TMS pulses delivered per second.

  Depending on the frequency, rTMS is subdivided into "**low-frequency rTMS** (lf-rTMS)" when delivered at < 1 Hz, and "**high-frequency** rTMS (hf-rTMS)" when set > 1 Hz, usually 5-25 Hz (35,39). Recently new rTMS frequency protocols have been developed. They are called patterned rTMS and the most common is the theta-burst stimulation (TBS), which consists of a low intensity burst triplet at 50Hz (3 pulses with 20ms of inter-pulse interval) repeated at 5Hz (38). TBS can be divided into "continuous TBS" (cTBS) o "intermittent TBS" (iTBS) (35), depending on the absence or the presence of a non-stimulation period in between pulses (Figure 12). That is important because different frequencies produce different effects: cTBS and lf-rTMS protocols produce inhibitory aftereffects and iTBS and hf-rTMS increase cortical excitability (35,38,40).

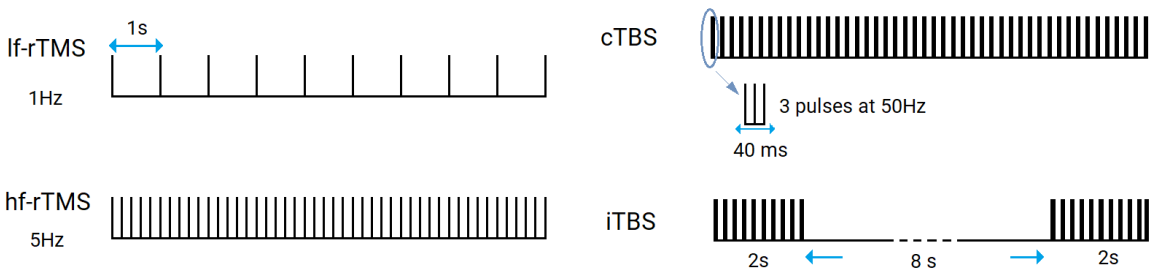


Figure 12. Repetitive TMS (rTMS): low-frequency (lf-rTMS, 1Hz), high-frequency (hf-rTMS, 5Hz), continuous TBS (cTBS) and intermittent TBS (iTBS). Notice that each patterned pulse is composed by 3 pulses of 50Hz. Modified from Klomjai et al. 2015 (40).

- Number of pulses and number of trains. The number of pulses is proportional to the length of the train duration, and the number of trains determines the total number of pulses delivered in on session.

- Inter-train interval (ITI). Time between the delivery of two consecutive trains.

- Types of coils. Various types of coils with different shapes and sizes have been developed: circular coil, figure 8 coil, double cone, air-cooled coil, c-Core coil, circular crown coil and H-coil (40) (Table 3). Circular coils are recommended for stimulation of large and superficial areas; Figure 8 coils produce more focalized stimulation and double-cone coils reach deeper brain layers. Figure 8 coils only reach 1.5-3cm beneath scalp so they cannot stimulate subcortical structures (35); new developed coils such as C-coils, H-coils and circular-crown coils, instead, can reach these areas (35,40).

Table 3. Types of coils.

CIRCULAR	FIGURE-8	DOUBLE-CONE	H-COIL
			

Clinical possibilities of rTMS

Clinical trials, systematic reviews and meta-analysis have emitted favourable recommendations on rTMS for a variety of conditions: **depression** (41), bipolar disorder, **AD** (42,43), **Parkinson's disease** (44,45), dementia with Lewy's Bodies (46), MCI (47,48), **obsessive-compulsive disorder** (49,50), autism (51), schizophrenia (52); **post-traumatic stress disorder** (53) and **post-stroke** aphasia (54), motor skills impairment (55) and dysphagia (56). It has also been assessed on chronic pain (57), panic disorder, tobacco and cocaine craving (37).

Although this variety of possibilities, according to the "2016 Spanish report on sanitary technologies evaluation" (37), most of the findings are inconsistent due to methodological differences used to measure outcomes, the heterogeneous experimental designs, the different targeted brain regions and variable rTMS parameters (36). Therefore, the level of evidence of most of these recommendations is low and further controlled and randomized studies comparing protocols are needed to prove all these preliminary results.

On 2008, rTMS was approved by the US Food and Drug Administration (FDA) for the treatment of medication-refractory major depression syndrome (58). Spain government also approved rTMS on this indication, when no other therapeutic options are available and discussing with the patient the decision to whether apply electroconvulsive therapy (ECT) or rTMS (37).

Although these cautious recommendations, some private clinics such as Guttmann Institute (Badalona), López Ibor (Madrid), Clínica San Vicente (Madrid), Neurocavis (Madrid), Hospital Delfos (Barcelona), Neurofisiología Clínica Isabel Goirigolzarri (Bilbao) and others are already offering rTMS as treatment for other conditions such as post-stroke aphasia, obsessive-compulsive disorder (OCD), MCI, bipolar disorder, post-traumatic stress disorder, multiple sclerosis, tinnitus, migraine, schizophrenia and drug-resistant depression; reporting positive results.

rTMS and empathy

Besides all these potential uses, rTMS capability of enhancing empathy has also been studied. Yang *et al.* (2017) published a meta-analysis on the effects of rTMS on empathy (36), reviewing articles that mostly were performed on healthy volunteers (51). They observed a positive but small size effect on the overall analysis, but when subgroup analysis was performed, they found a moderate effect size on enhancing cognitive ToM when high-frequency (excitatory) rTMS was used. When discussing its limitations, Yang *et al.* argued that TMS-response is dose dependent and most of the studies analysed performed rTMS on just a single session, so probably larger number of sessions and pulses may be required to modulate empathy better. They also pointed out that baseline empathy level was not investigated, and it could have a role on determining rTMS response. This suggests that rTMS could be more useful on people suffering from empathy impairment at baseline and using multiple-sessions treatment plans.

rTMS and FTD

At this date, only one open-label study has assessed rTMS on FTD population. Antczak *et al.* (2018) (59) assessed the effects of 10-days 10Hz rTMS on global cognitive impairment in 11 patients with FTD, 9 of them with bvFTD. They targeted DLPFC and delivered rTMS at 90%MT totalling 3000 pulses/session. They found a significant improvement on Montreal Cognitive Assessment (MoCA), Stroop test, the Digit Cancellation test, and the Frontal Behaviour Inventory (FBI), but they lack from a controlled condition and the sample size was very small.

Another study has assessed tDCS effects on cognitive ToM in bvFTD. Cotelli *et al.* 2018 (60) designed a placebo-controlled, randomized study on 32 patients targeting the medial prefrontal cortex. They found a small significant effect ameliorating the performance of the task.

These results illustrate a theoretical potential of NIBS for improving empathy in bvFTD patients but is obvious that further investigations using larger samples and controlled conditions are needed.

Safety concerns and side effects

Safety guidelines must be followed in order to avoid seizures and other side effects (Annex 4). On 2009, the International Federation for Clinical Neurophysiology (IFCN) published the safety guidelines for TMS use (35), and these are the ones currently approved by FDA. Here are summarized the most important concepts:

Safety measures

- Metal and electronic devices. TMS is contraindicated in possession of electric/magnetic implanted devices inside or near head. Preferentially there should be > 30 cm between the coil and any metal/electronic device. Jewellery, glasses, watches and other potentially conducting objects should be removed during stimulation.
- Hearing protection. Hearing protection is required during the use of rTMS devices. Patients and operators should always wear earplugs or similar.
- Medication assessment. Is recommendable an accurate assessment of the concomitant drug intake during TMS as some medication increase the risk of seizures.
- Staff safety. The safety of chronic exposure to electromagnetic field is unclear. It is recommended to avoid exposure closer than 40cm from the coil.
- Vulnerable populations. There is a lack of evidence on pregnant women and population <18 years-of-age; therefore risk-benefit should be discussed on these populations.

Side effects

TMS is a safe and well-tolerated technique (61). Common side effects are mild and include local pain, transient headache neck pain, toothache and paraesthesia; serious adverse effects are rare and include hear loss, seizures, psychosis and/or affective switch and syncope (61).

- **Local pain**. It is attributed to stimulation of superficial nerves and/or the contracture of local stimulated muscles. Although has 40% of frequency, less than 2% of clinical trial participants discontinue the treatment due pain. It rapidly vanishes after stimulation and in general, improves over the course of treatment due tolerance development (35).
- **Transient headache**. Caused by local scalp stimulation or changes in cerebral blood flow. It has an estimated 25% of incidence and it can be managed with simple analgesia.
- **Neck pain**. Related to prolonged uncomfortable position during the session (35).
- **Hearing impairment**. Practically inexistent risk when hearing protection is wore (35).
- **Seizures**. When following safety guidelines, the estimated overall risk of seizures is very low (<0.1%) (41). Risk increases on hf-rTMS, pre-existing neurological conditions, substance abuse and changes in concurrent medications. Longer ITIs protect from seizures. All reported seizures were self-limited and occurred during the treatment session (35,41) and most of them occurred on pro-epileptogenic conditions[2].

[2] Pro-epileptogenic conditions: family history of epilepsy, brain lesions, pro-epileptogenic medication

- **Affective switch and psychosis**. The risk of maniac/hypomanic switch appears to be low (0.84% of incidence) and mostly reported on depression or bipolar patients (35).
- **Vasovagal syncope**. It is not considered to be related to therapy, otherwise as a reaction to anxiety and psychophysical discomfort (35).
- **Cognitive change**. TMS can make subjects perform better (excitatory rTMS) or worse (inhibitory rTMS) on a given task (35).

There have been reported other possible side effects, which its casualty is not elucidated, such as **retinal tear** (single case report, without clear casualty relation) (62), **endocrine-aftereffects** (one placebo-controlled study – Evers *et al.* 2001 – reported TSH and cortisol decrease after subthreshold stimulation rTMS), acute changes in **neurotransmitters** (dopamine, glutamate and others) and **autonomic alteration** (35).

2.2. Justification

The increase in life expectancy and decrease in natality rates are resulting in a progressive aging of the population, and consequently, an increment of diseases that specially affect old people. Dementias are one of them (11).

Dementias are acquired syndromes that cause a progressive global deterioration of intellectual functions, interfering in daily living activities and diminishing personal autonomy (1). They represent one of the main causes of disability and are the leading cause of dependency in later life (11). Nowadays, 6.5% of the population over 64 years suffer from dementia (3), and it is estimated that 152 million of people will develop this pathology on 2050, threatening the sustainability of the public health system (11).

There is still a lack of awareness and understanding of dementia and the few available therapies are far from being able to significantly improve the disease course nor offering a cure (4). Although lots of efforts have been made to develop new options, most of them have failed proving real and clinically meaningful benefit; generating certain desperation on the scientific community.

A clear example are the acetylcholinesterase inhibitors, considered the first line treatment for AD, which showed to reduce cognitive decline only in a small-moderate effect size, but did not report any benefits on more important factors such as institutionalization rates or survival (63). Only one breaking new on 27th October 2018 brings hope to dementia research: the AMBAR study (Alzheimer Management By Albumin Replacement) from Grifols company (64), based on removal of the beta-amyloid from brain through plasmapheresis (65), showed a significant reduction (61%) on moderate AD progression.

Frontotemporal dementia represents the second cause of early-onset dementia (17) and affects personality, language and/or executive abilities (1). Empathy loss is one of the core features its behavioural variant (21), which is manifested as lack of affectivity, impaired emotional recognition and inappropriate social response. Consequently, their relationships become disrupted and their caregivers and familiars experiment incomprehension and lack of warmth, increasing their burden and reducing their quality of life (24,66).

Social impairment is not surprising on these patients as it is well-known that frontal and temporal lobes have important roles on empathy function (26,29). Numerous brain networks participate on the production of this multifactorial and complex ability, but vmPFC specially stands outs above

the others. This area is fundamental on affective ToM, and links *thoughts* and *feels* through connections with the amygdala and other limbic system structures (29).

Although bvFTD is less common than AD, it disproportionately affects younger patients, producing a major psychological and economic burden for patients and their families (2). It is not preventable because its risk factors are mostly genetic (17), and has a life expectancy of only 7-10 years (17). Nowadays no therapy is approved for its treatment, which limits its management to educational and symptomatic measures (17).

Lots of medications have been tried for FTD. Donepezil showed no changes in cognition and worsened behavioural symptoms (67,68), and galantamine did not prove any benefit neither (69). Other studies suggested positive results reducing behaviour alterations and apathy using rivastigmine (70), memantine (71) and agomelatine (72), but they are based on small samples sizes and their statistical effect, although significant, is usually small and assessed on subrogate variables. Therefore, the evidence on the possible clinical benefit of this therapies is low and uncertain, far from being promising and without chance to modify the progression of the disease.

tDCS has been assayed for ToM impairments and anomia, on bvFTD (60) and PPA (73), respectively, theorizing a potential benefit of this technique, but further studies are needed. Oxytocin is also being trialled and seems to improve social cognition and behavioural symptoms (74), but for now effects look to be short-lasting.

Other medications currently on trial are (75): tolcapone, TRx0237 (tau protein aggregation inhibitor), FRM-0334 (histone deacetylase inhibitor), BIIB092 (IgG4 monoclonal anti-tau antibody), AL-108 (neuropeptide derived from activity-dependent neurotrophic protein), infrared radiations and lithium. Some of them are trying to demonstrate neuroprotective properties, but large time will be needed to publish their results and demonstrate its benefits.

Among all these theoretical possibilities it is found rTMS. It is an non-invasive, low-cost, safe, easy to apply and available technique (35) that is emerging as a potential therapy for multiple neurologic and psychiatric pathologies such as depression, Parkinson's disease, post-traumatic stress disorder, AD and post-stroke aphasia (35). On 2008, FDA approved its use for drug-resistant depression and emitted a control and safety guidelines. Moreover, rTMS has also been applied to increase empathy and cognition in healthy population and dementia, respectively, with promising results (36,76), suggesting that it could become a possible therapy to enhance social cognition on people suffering from bvFTD.

Only one fact limits its applicability: the lack of studies comparing different rTMS protocols. Few studies compare rTMS parameters, so the most effective protocol has not been uncovered. To try to solve this inconvenient and elucidate if rTMS could be a therapeutic tool for bvFTD, two different stimulation parameters will be trialled in this study, defining which is the most effective and could be executed in the current clinical practice.

Although rTMS won change the natural course of bvFTD, it may bring a better life to bvFTD patients and their families.

3. HYPOTHESIS

The hypothesis of this study is that repetitive transcranial magnetic stimulation can improve empathy in behavioural variant frontotemporal dementia when compared to sham stimulation, and that one of the two stimulation parameters could be superior to the other, standing out for future controlled studies.

4. OBJECTIVES

4.1. Main objective

The fundamental purpose of this study is to compare subthreshold rTMS (90% MT), suprathreshold rTMS and sham-stimulation, applied on bilateral orbitofrontal cortex, and assess if rTMS may improve empathy on people suffering from bvFTD, and which intensity shows the best effect size; after 4 weeks, 6 months and 1 year from stimulation.

4.2. Secondary objectives

Other objectives set for this trial are:

- To evaluate the efficacy on decision-making (Iowa Gambling Task, IGT).
- To study the improvement on neuropsychiatric symptoms, assessed by the neuro-psychiatric inventory scale (NPI).
- To assess if empathy improvement on bvFTD patients traduces to a better caregivers' quality of life.
- To observe the efficacy of both protocols for the enhancement of other cognitive areas usually impaired in dementias and particularly in bvFTD patients; such as orientation, memory, language, executive functions and attention.
- To determine difference on global clinical improvement appreciated by caregivers.
- To study the if the degree of atrophy assessed using MRI can influence the effect of rTMS on empathy and other neurocognitive domains.
- To investigate if sex and age are variables interfering with the results.
- To register the tolerability of the process, the incidence of adverse effects and any differences regarding safety concerns between the two stimulation intensities.

5. MATERIAL AND METHODS

5.1. Study Design

The study will be a randomized, single-blinded, sham-controlled clinical trial. It will be conducted in 7 centres of Girona, Barcelona, San Sebastián, Bilbao and Madrid. The total length of the clinical trial phase will be approximately 2 years.

5.2. Target population

The target population will be people diagnosed from "**probable bvFTD**" according International Consensus Criteria (21) (Annex 2), of both genders, without exclusion of age, living in the sanitary region of Girona, Barcelona, Bilbao, San Sebastián or Madrid, whom are in early stages of the disease.

The incapacity to understand the tasks due a large cognitive impairment, late stage of dementia or other conditions would suppose a problem to perform the neuropsychological and empathy tests and correctly interpret the results; thereby this population will be out of the trial.

Seizures are a well-known serious adverse effect of rTMS; therefore, patients with a positive history of seizures or epilepsy will not be included. Substance abuse and change in medication can increase the seizure risk (35); so, those who changed pharmacology 2 weeks before the start of the trial and the ones abusing on substances will be excluded. Change in medication during the treatment will not be allowed.

Patients who have brain lesions such as major head trauma, brain surgery and/or brain tumour will be also excluded due to the possible interference with the efficacy of rTMS (43).

Having a brain implant or electronic or metal device inside head or ≤ 30 cm near hear it is a contraindication to perform rTMS (61). Therefore, cochlear implants, aneurism clips, stents, ocular implants and deep brain electrodes are contraindicated (35). Although carrying pacemakers and other devices far from stimulation site is assumed to be safe, these patients will be excluded for security concerns.

Furthermore, patients who already suffered from a noise induced hearing loss or under ototoxic medication will be excluded.

5.2.1. Inclusion criteria

- Meeting FTDC (International bvFTD Criteria Consortium) criteria for "provable bvFTD"
- Presence of minimum one caregiver responsible for the patient's adherence to therapy
- Signed informed consent (Annex 5)

5.2.2. Exclusion criteria

- Pregnancy or lactation
- CDR 2 o 3 or other condition impairing empathy tests performance
- History of seizures
- Acute psychosis or history of bipolar disorder
- Substance abuse or dependency (alcohol, caffeine, other drugs)
- Pharmacology changed 2 weeks before the start of the study
- Major head trauma, past brain surgery and/or brain tumour
- Pre-existing noise induced hearing loss or concurrent treatment with ototoxic medication (aminoglycosides, cisplatin)
- Metallic, ferromagnetic objects or electronic devices in or near (≤ 30 cm) head
- Pacemaker, cardioverters defibrillators, pumps and intracardiac lines
- Personal history of prior use of tDCS or rTMS

5.3. Sampling

5.3.1. Sample size

The sample size has been calculated using GRANMO free application (77).

There are no previous references regarding the expected clinical differences on RMET using rTMS in bvFTD. However, Torralva T. *et al.* (2009) (31) provided useful statistical data (mean and standard deviation) of some empathy tests when performed by bvFTD patients compared to healthy age-matched population. Also, Baron-Cohen *et al.* (2001) (32), De Achával *et al.* (2010) (78) and Redondo I. *et al.* (2018) (79) provide standard deviations of RMET when applied to healthy population (SD ≈ 3.5), adults with high-functioning autism (SD ≈ 6.6), patients with schizophrenia (SD ≈ 5.4) and population with anorexia (SD ≈ 2.1).

Using the information from literature review, it has been assumed a standard deviation of 3.5 because it corresponded to the SD of the subgroup with the largest N size (healthy adults). The minimum expected difference is estimated to be 2 point in RMET scoring. It has been accepted an alpha risk of 0.025 –half the standard risk as it is a three-arm trial – and a beta risk of 0.02. A drop-out rate of 15% has been anticipated.

GRANMO results show a sample size of 51 participants in each arm. Therefore, the total number of subjects will be **153**.

5.3.2. Sample selection and enrolment

A non-probabilistic consecutive sampling method will be used. Patients fulfilling the inclusion and exclusion criteria will be selected as they are admitted in the different participating centres. Patients will be collected from Neurology Departments of the enrolled centres, either being the first visit or a consecutive follow-up context. Candidates will be informed about the study with the Study information Sheet and invited to voluntarily participate by signing the informed consent (Annex 5). The sampling will be conducted until the sample size is correctly completed.

5.3.3. Estimated time of recruitment

The approximated time of recruitment will be 1 year. It has estimated according to bvFTD incidence in the sanitary region of Girona. There are diagnosed 19 new cases of bvFTD every year in a population of 740,004 inhabitants (20), so the incidence is 2.57 new cases per year.

Table 4 shows the inhabitants of the different participating centres areas and their estimated contribution to the sample size, according to Girona's bvFTD incidence.

Table 4. Estimated number of participants recruited in each area per year.

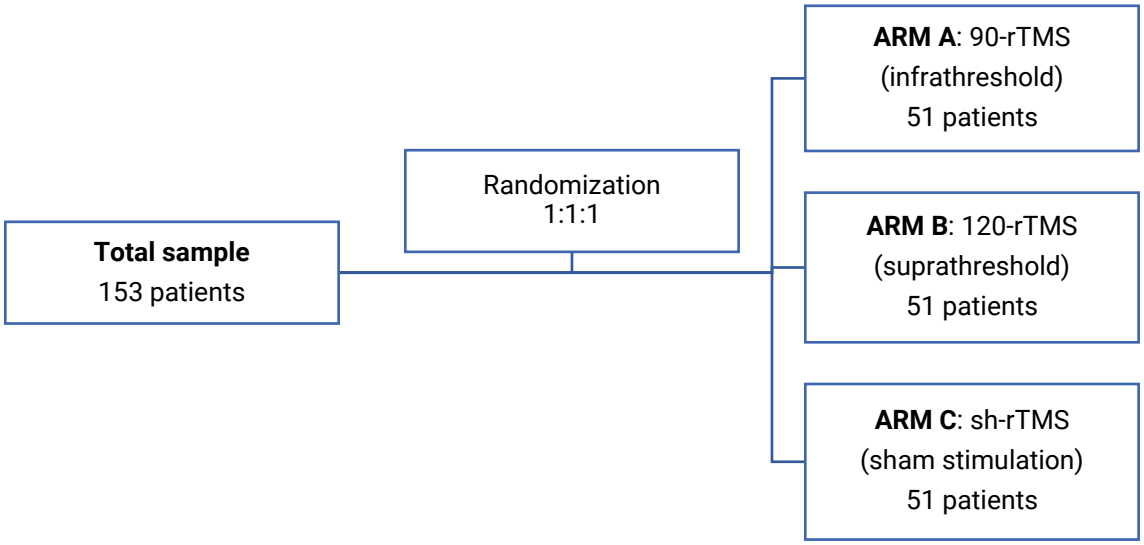
City (area)	**Population** (persons)	**Estimated sample recruitment**
Girona (sanitary region)	740,004	19
Barcelona (city)	1,609,000	41
San Sebastián (metropolitan area)	444,152	11
Bilbao (metropolitan area)	1,037,847	26
Madrid (city)	3,166,000	81
	TOTAL	**178**

The new diagnosticated cases of bvFTD in one year on those regions are estimated to be **178**. Not all of them will fulfil the inclusion and exclusion criteria, but other bvFTD patients, already diagnosed years before, will attend those centres, so the sample will be larger.

5.3.4. Randomization and masking

Patients will be randomly allocated to one of the groups: a) sub-threshold rTMS (90-rTMS), b) supra-threshold rTMS (120-rTMS) and c) sham stimulation control group (sh-rTMS). They will be randomized into the three arms following a 1:1:1 ratio.

Randomization will be performed by an independent company after the successive enrolment of participants. The allocation will be hidden from participants and from neurologists, radiologists and neuropsychologists performing the correspondent clinical evaluations and follow-up. However, randomization will be revealed to the technical neuro-physiologists conducting the stimulation due the impossibility to blindly conduct the intervention.



5.4. Variables and measurements

5.4.1. Principal variables

Independent variable

- Type and intensity of stimulation. According to the randomization outcome it will be delivered 90-rTMS (arm A), 120-rTMS (arm B) or sh-rTMS (arm C). The following table summarizes the differences on stimulation parameters among the study's arms.

Table 5. Study's arms and its correspondent parameters of stimulation.

	TYPE OF STIMULATION		
	ARM A 90-rTMS	**ARM B** 120-rTMS	**ARM C** sh-rTMS
Type of device	70-mm figure-8 coil		
Coil positioning	Fp1, Fp2	Fp1, Fp2	Perpendicular to Cz (sham stimulation)
Intensity	90% MT (subthreshold)	120% MT (suprathreshold)	90% MT (subthreshold)
Frequency	10 Hz	10 Hz	10 Hz
Pulses per train	50	40	50
Duration of trains	5 sec	4 sec	5 sec
Total nº of trains	28	35	28
ITI	25 sec	30 sec	25 sec
Total nº of pulses per session	2800 total pulses per session (1400 pulses/side)		
Duration of each session	30 min	40 min	30 min

a. **Type of coil**. The stimulation will be delivered with a 70-mm figure-8 coil device.

b. **Coil positioning**. On active stimulation groups (arm A and B), the targeted cortex will be bilateral OFC. The coil will be positioned over the Fp2 (right) and Fp1 (left) EEG sites for the right and left OFC, respectively, defined according to the international 10-20 system (See Annex 6 for detailed EEG positioning). Fp2 and Fp1 have the greatest anatomical correlation to medial OFC according to literature review (80,81). It will be stimulated first the left side and then the right site in every session. On the sham group (arm C), the coil will be positioned on the vertex of the brain (Cz) perpendicular to scalp, reproducing the sound but without any effects on

OFC. This method was already used before as a sham-stimulation (82). Figure 13 illustrates the EEG positions on 10-20 system and the placement of the coil during the active stimulation.

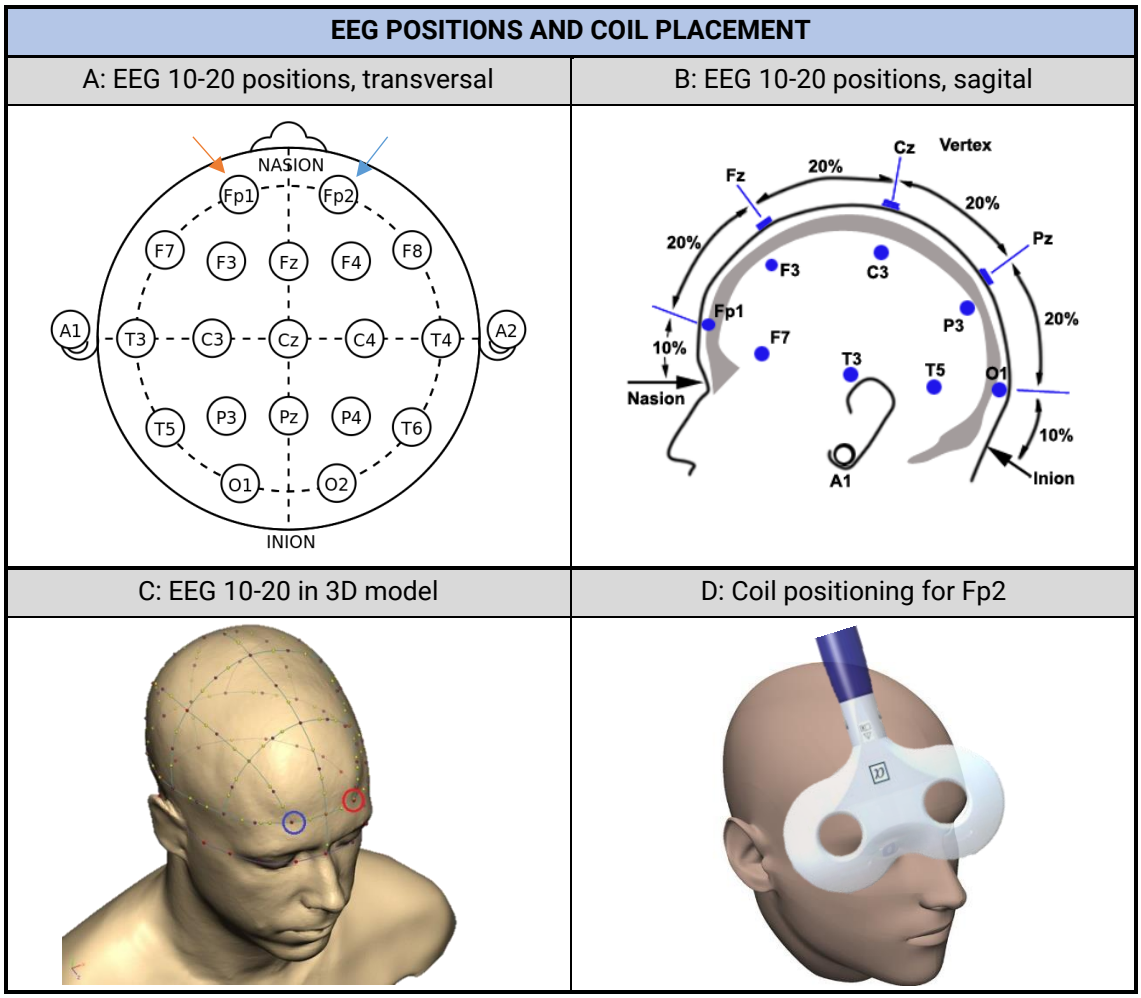


Figure 13. EEG 10-20 international system and coil positioning. A) From: "Wikimedia Commons – 10-20 EEG " (83)*, B) from "McGil Virtual Labl"* (84)*, C) from "Three Form Fashion"* (85) *and D) modified from "Clipart Library" and "Medical Expo"* (86,87)*.*

c. **Frequency**. It will be 10 Hz among the three arms.

d. **Determination of MT**. A single pulse TMS will be applied on the primary motor cortex (M1) with the coil oriented laterally (i.e. handle perpendicular to midline, and current flow toward the hemisphere to be stimulated), to activate abductor pollicis brevis. The motor activation will be assessed by superficial electrodes recording MEPs (39).

e. **Intensity**. Expressed as % of MT. This value will differ according to the arm of the trial: arm A) 90% of MT (subthreshold); arm B) 120% of MT (suprathreshold) and arm C) sham stimulation, at 90% of MT.

f. **Pulses per train and total number of trains**. It will depend on the arm: A) will receive 28 trains of 50 pulses each one; B) 35 trains of 40 pulses per train and C) 28 trains of 50 pulses. The duration of one train correlates to the number of pulses per train.

g. **ITI**. This parameter will also vary among the different arms: A) ITI = 25 seconds, b) ITI = 30 seconds and C) ITI = 25 seconds.

h. **Total pulses per session**. In every session, 1400 pulses will be delivered to each OFC (in total 2800 pulses/session).

i. **Duration of the sessions**. The session will last approximately between 30 min and 40 min. Patients will receive a total of 20 sessions, delivered as 1 session per day, 5 session per week. The hole intervention will last 4 weeks.

Dependent variable

- Emotional and cognitive empathy. It will be evaluated using the Spanish adult version of the revised RMET, Baron-Cohen *et al.*, 2001 (32), translated and adapted by Huerta E. and Ferrer, 2016 (88)[3]. As mentioned before, this empathy test is constituted by 36 grey-scale photos showing the ocular region of a person, each one surrounded by four mental state terms. The subject will be asked to choose the word better describing what the person of the photo is thinking or feeling, and only one answer is considered correct. It will be provided also a definition handout for vocabulary consulting, that can be used for the subjects when they do not understand the exact meaning of a word. It must be done as quick as possible, but subjects will not be timed. Responses will be coded as 0 (incorrect) and 1 (correct), and main outcome will be RMET total score (from 0 to 36).

5.4.2. Secondary variables

- Cognitive empathy (ToM). It will be evaluated using the Spanish version of FxP – Stone *et al.* (1997) and Gregory *et al.* (2001) (30,34)–, adapted and translated by Serrano C. (Buenos Aires) (88)[4]. FxP is formed by 20 stories of which 10 contain a social faux pas. The evaluator will read aloud the story and the text will be placed in front of the patient to avoid interferences of working memory during the evaluation. At the end of each story, it will be formulated the 8 pertinent questions (not-showed to the patient). It will be scored

[3] Available on: https://www.autismresearchcentre.com/arc_tests

1 point for every correct answer and 0 for incorrect ones. In case of control stories, the subject will get 1 point for non-answering questions from 2 to 6. As explained, each question has a different purpose and the scoring must be reported separately (see Annex 7 for full scoring information). If the subject fails on the control questions, the responses to the questions of that story will not be counted. The principal outcome measure will be the number of correctly detected *Faux Pas* and non-*faux pas* stories (from 0 to 20).

- Decision-making capacity. It will be evaluated using the Iowa Gambling Task (IGT, Bechara et al 1994) (89). This test mimics real-life decision making. It is an informatic software in which participants are asked to continuously select cards from 4 decks (A, B, C, D) in order to make as much money as possible. Decks A and B are ultimately risky (large rewards and large punishments) and C and D are more conservative (small rewards and penalties). Task finishes at 100 selections. Net earnings are only feasible selecting from low efficient decks. The outcome measure will be the Net Score = number of selected (C+D) – (A + B). To quantify the progression during the task the score is split into 5 blocks of 20 consecutive choices.

- Neuropsychiatric symptoms. The presence of neuropsychiatric symptoms will be assessed using the Spanish translation (Vilalta-Franch, 1999)[4] (90) from the Neuropsychiatric Inventory (NPI-10) (Cummings *et al.* 1994) (91). NPI examines 10 behavioural disturbances occurring in dementia patients: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor activity. Both the frequency (from 0 to 4) and intensity (from 1 to 3) of each group of symptoms are determined. Information for the NPI will be provided by the caregiver during the personal interview. The final score will be calculated multiplying frequency × intensity and summing up all the results from all behaviour domains (maximum 120 points).

- Caregivers' quality of life. It will be assessed using the Spanish adaptation (Carrasco M. 1996) (92)[5] of Zarit Burden Interview (ZBI) for caregivers (Zarit 1980) (93) and also through the subjective reports of the caregivers' and clinical observations. ZBI has been

[4] From http://npitest.net/
[5] Available on http://www.hipocampo.org

specially designed to reflect the stress experienced by caregivers of dementia patients. It will be administered during the caregiver's interview. The carer will be asked to respond to a series of 22 questions about the impact of patient's disabilities on their life. Each item is rated according to the frequency that caregivers feel that way (never = 0, rarely = 1, sometimes = 2, quite frequently = 3 or nearly always = 4). The total score ranks from 0 to 88. Higher scores are indicative of greater caregiver stress; more than 56 is considered intense distress level.

- General cognitive status. It will be recorded using the Spanish validated adaptation (Lobo *et al.*, 1979)[6] of the Mini-mental State Examination (MMSE) (Folstein *et al.* 1975) (94), which is fast to administrate and is world-wide standardized. It ranks from 0 to 30 and it assesses 5 cognitive areas: orientation (0-10 points), registration (0-3 points), attention and calculation (0-3 points), memory recall (0-3 points) and language and praxis (0-9 points). It is considered abnormal < 24 points.

- Language. The word naming ability will be assessed using the Spanish short version (Fernández-Blázquez, 2012) (95) of Boston naming test (BNT, Kaplan *et al.* 1983) (96) and the language fluency using the semantic verbal fluency test.
    - The **15-BNT** consists of 15 line-drawing items from different grade of familiarity. The patient is asked to name the picture in a 20 seconds maximum time. The evaluator can give a phonemic clue (the initial phoneme) to the patient.
    - In the **semantic verbal fluency** test subjects are required to produce as many words pertaining to the "animals" semantic category during a 60 seconds time. The number of words produced will be the scoring.

- Executive functions. Frontal Assessment Battery test (FAB-test), Dubois et al (2000) (97), includes 6 subtests: conceptualization, mental flexibility, motor programming, sensitivity to interference inhibitory control and environmental autonomy. Each category can score a maximum of three points and the total score is expressed maintaining the different blocks separated (e. g. 2-1-3-3-0-2). It will be used the Spanish version, Rodriguez del Alamo, A. (2003) (98).

[6] From ICS guides https://www.ics.gencat.cat/3clics/guies/30/img/minimentaldef.MMSE.pdf

- Attention and concentration. This domain will be assessed using the Trail Making Test A (TMT-A) and B (TMT-B) (Partington and Leiter, 1949) (99)[7]. In TMT-A the participant is asked to connect as quickly as possible randomly arranged circles containing numbers from 1 to 25 following the number sequence. TMT-B, otherwise, contains numbers from 1 to 13 and letters A to L. The respondent will have to connect in order the circles alternating numbers and letters (e.g. A-1-B-2-C-3). Before starting the test, a practice trial of 6 items will be administered. The maximum administrating time is 5 minutes. The outcome scores are the total time (minutes) used to complete each part.

- Global clinical improvement appreciated by caregivers. It will be collected during the caregiver's personal interview as subjective information. This data will not be included in the statistical analysis, and it will be used to pick up the caregiver's impressions on participants general status.

- Side effects. Every side effect occurring during the rTMS session or in the days later which meet the Bradford Hill criteria of causation (1965) will be collected in a table expressing the total number of patients who experimented the adverse effect, and then the incidence will be calculated. It will be reported both already known adverse effects and possible related side effects not classically described. The local pain produced during the stimulation will be evaluated using a numeric rating scale from 0 (no pain) to 10 (maximum tolerable pain). The common adverse effects are headache, local pain and neck pain. Other exceptional side effects are hearing loss, seizures, syncope and acute psychiatric changes.

5.4.3. Covariables

- Dementia severity. The degree of cognitive impairment will be evaluated using the classification of the Spanish version (Sociedad Neurológica Argentina[8]) of the Clinical Dementia Rating (Hughes *et al.* 1982) (100). It assesses memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care, using the caregiver's information. Patients scoring CDR 2 (moderate dementia) or CDR 3 (severe dementia) will be excluded from the study.

[7] Available on http://www.nmr.mgh.harvard.edu/~bradd/Trail_Making_Test.pdf
[8] Available on http://www.sna.org.ar/web/admin/art_doc/194/CDR_de_Hughes.pdf

- MRI atrophy degree at the time of diagnosis. It will be expressed using two different MRI scales (Annex 8). As there is no radiologic scale assessing frontal atrophy, the global cortical atrophy scale (GCA) and the Medial Temporal lobe atrophy scale (MTA) will be used[9]. GCA is the mean score for cortical atrophy throughout the complete cerebrum and it rates the atrophy from 0 to 3, reporting the absence or presence of asymmetry. GCA will be scored on FLAIR images. MTA-score will be rated on coronal T1-weighted images, and it is based on a visual rating of the width of the choroid fissure, the width of temporal horn and the height of the hippocampal formation. Score gets from 0 to 4. Participants will be stratified in two groups to perform secondary analysis: (A) GCA 1 or 2 and (B) GCA 3, for GCA and (A) MTA 1 or 2 and (B) MTA 3 or 4, for MTA.

- Personal history. It is necessary to assess the psychiatric history, ask for electric/ magnetic devices, pre-existing hearing impairment and/or substance abuse or dependence, as well as other important information regarding safety. This data will not be included in statistical analysis.

- Concomitant treatments. All the medications that are being consumed will be reported to assess the possible interactions and synergies between medication and rTMS. As far as possible, pro-epileptic medications must be changed for other available options. Medication for neuropsychiatric symptoms and other possible interfering drugs will remain unchanged 2 weeks before and during the whole intervention. This data will be not considered in the statistical analysis.

- Sex. Recorded as F (female) for women and M (male) for men.

- Age. Recorded as years of age.

[9] From http://www.radiologyassistant.nl/en/p43dbf6d16f98d/dementia-role-of-mri.html#i445b139abe503

6. DATA COLLECTION

Data recorded from participants at baseline and during the following visits will be registered and submitted to a database shared within all centres. To preserve anonymity and keep the blind during the study, every patient will be assigned with a specific identification code. The results of all the neuropsychological tests will be also physically stored labelled with patients' codes.

6.1. Visit schedule

Period 1: screening and baseline measures

Week -2: once a participant meeting the inclusion and exclusion criteria is identified, the study will be proposed. If interested, it will be provided the study information sheet (Annex 5) and the neurologist will explain and comment it. If the patient agrees, he/she will sign the informed consent and fulfil the personal data in the collection sheet. Next visits will be scheduled.

Week -1: in this period, the participant will perform a brain MRI and will undergo the basic neuropsychological tests (MMSE, BNT, verbal fluency test, FAB-test, TMT-A and TMT-B). It will also be performed the personal interview with the principal caregiver assessing CDR, NPI and ZBI.

Although belonging to baseline measures, the rest of the neuropsychological tests will be performed on week 1 due the impossibility to carry out all the test in one day with a reasonable toleration level for the patient. MRI is routinely done during the diagnostic procedure of dementias, so it could be possible that the patient has already an available MRI. If the participant has a recent MRI (< 6 months), it will not be necessary to perform a new one as it is assumed that changes in brain atrophy will be minimal.

Week 0: randomization and assignment of the patient to one of the study's arms.

Week 1: after the randomization and prior to the stimulation, the participant will perform the remaining neuropsychological tests (RMET, FxP and IGT).

Period 2: Intervention period

Week 1 – week 4: for one month, participants will receive 1 session/day only on working days (5 sessions/week). Depending on the assigned group, the stimulation will be 90-rTMS, 120-rTMS or sh-rTMS. At the end of every session, the possible side effects will be reported and collected. In

the middle of the intervention period (end of week 2), tests assessing empathy (RMET and FxP) and NPI from caregiver will be performed again. At the end of the stimulation period, all the neuropsychological tests will be delivered during two consecutive days, following the structure previously used. It will be also be recorded the NPI reported by the caregiver.

Period 3: Follow-up

To assess the long-term intervention impact and the maintenance of the effect, 4 follow-up visits will be scheduled: 2 on month 6 and 2 at the year. In these visits, all the neuropsychological test will be assessed again among two consecutive days. One personal interview with the caregiver per check-point will also be done to assess NPI and ZBI. Also, it will be recorded any possible long-term adverse effect.

The following table summarises the visits schedule and the timing of the data collection:

Table 6. Visit schedule and collected data during all the trial

		Baseline measures							Follow-up							
					Intervention											
		Weeks							Months							
Appointment		-2	-1	0	1	2	3	4	2	3	4	5	6	8	10	12
Information sheet and informed consent		X		Randomization												
Age, sex, medication, personal history		X														
MRI			X*													
rTMS session					X	X	X	X								
Specific battery	RMET				X	X		X					X			X
	FxP				X	X		X					X			X
	IGT				X			X					X			X
Basic battery	MMSE		X					X					X			X
	BNT		X					X					X			X
	Verbal fluency		X					X					X			X
	FAB-test		X					X					X			X
	TMT-A, TMT-B		X					X					X			X
Personal caregiver's interview	CDR		X													
	NPI		X			X		X					X			X
	ZBI		X					X					X			X
Side effects					X	X	X	X					X			X

X*= only if there is not a recent MRI (<6 months) already performed

6.2. Tasks' assignment

Data will be collected by the research team and assigned according to their discipline (Table 7). The neurologists will be responsible of the patient recruitment, information and consent. The neuropsychologists will perform the cognitive tests and the personal caregiver's interview during the intervention and follow-up visits. The radiologist will evaluate the MRI atrophy. Finally, the rTMS sessions and the evaluation of the possible side effects will be done by the neurophysiologists.

Table 7. Assignment of tasks

Study member	Collected data
Neurologist	Information sheet and informed consent
	CDR
	Age, sex, medication, personal history
Neuropsychologist	Neuropsychological tests
	Caregiver's personal interview information
	NPI, ZBI
Neurophysiologist	Side effects during stimulation sessions
Radiologist	MRI atrophy degree

All the data collection process will be monitored by an independent organization to evaluate the quality and consistence of data.

7. STATISTICAL ANALYSIS

Statistical analysis will be performed using IBM Statistical Package for Social Sciences (SPSS) available for Windows® program.

For all analysis, a *p* value of < 0.05 will be defined as statistically significant and < 0.001 highly significant. Confident intervals will be expressed as 95%. Analysis will be performed using an intention to treat model. Missing data will be imputed using last observation carried forward (LOCF) strategy.

7.1. Variables definition

To perform the statistical analysis of the data, first variables will be defined as qualitative (categorical) or quantitative (numeric):

- **Independent variable**: the type of stimulation is considered a nominal qualitative variable (90-rTMS, 120-rTMS or sh-rTMS).
- **Dependent variable**: RMET outcome is assumed as a discrete quantitative variable.
- **Covariables**:
    - Discrete quantitative variables: cognitive empathy (total number of correct Faux Pas and controls stories), decision-making capacity (scoring of each block), neuropsychiatric symptoms (NPI final score), caregiver's quality of life (ZBI total score), executive function (scoring of each FAB subtest), local pain (numeric rating score), side effects (number of participants that experimented each adverse effect), age (years), general cognitive status (MMSE score), language (BNT and verbal fluency score).
    - Continuum quantitative variable: attention and concentration (spent time to perform TMT-A and TMT-B), side effects (incidence).
    - Ordinal qualitative variable: dementia severity (CDR 0.5/CDR 1), global cortical atrophy (GCA-1 and GCA-2/ GCA-3), medial temporal lobe atrophy (MTA 1 or 2/ MTA 3 or 4).
    - Nominal qualitative variable: drugs intake (name of every medication), brain atrophy (asymmetry/no-asymmetry on GCA scale), sex (female/male).

7.2. Univariate analysis

Univariate analysis will be performed in order to describe the sample.

Results will be expressed as frequencies (n) and/or percentages (%) for **categorical** variables. For **numeric** variables, it will be studied the variable distribution with Kolmogórov-Smirnov test. Variables with a normal distribution will be expressed as mean +/- standard deviation (SD) and those with a non-normally distribution the median and the interquartile range will be used. The quantitative variables will be showed as box-plot charts and qualitative variables with bar charts.

7.3. Bivariate analysis

- Principal analysis

Bivariate analysis will assess the homogeneity of the different study arms. The variables will be compared using x^2 test for proportions and ANOVA test for means and medians. Non-normal variables will be mathematically transformed to improve symmetry. If it is impossible to transform the variables to achieve better symmetry or conditions to perform ANOVA test are not applicable, Kruskal-Wallis test will be used.

To assess the impact of the different interventions on dependent and secondary variables, a bivariate analysis will be performed with data obtained at 4-weeks, 6-months and 1-year from the start of the stimulation. The same tests used to assess homogeneity will be employed. The variables included are the ones describe at the Data Collection section.

- Secondary analysis

It will be performed a secondary bivariate analysis taking MTA-score and GCA-score groups as the independent variable. Only dependent and secondary variables will be compared using ANOVA test. If ANOVA is not applicable, Kruskal Willis test will be used. Covariables' comparison will not be performed.

7.4. Multivariate analysis

As the study is a randomized trial, it is assumed that the possible confounding variables will be equally distributed; not expecting to perform a multivariate analysis.

To check for interactions between different variables we will use ANOVA multifactorial analysis.

8. ETHICAL CONSIDERATIONS

8.1. Ethical guidelines

This research protocol considers and applies the "Ethic Principles for Medical Research Involving Human Subjects" outlined in the World Medical Association Declaration of Helsinki (2013) (101), ensuring the preservation of human rights and ethical values. It also has been conducted respecting the "Guías de buena práctica clínica".

8.2. Clinical trial approval

Prior to the start of the study, the present protocol will be sent for consideration, comment, advice and approval to the Clinical Research Ethics Committee (CEIC) of "Hospital Universitari Josep Trueta" (Girona), as the leading centre and coordinator of the research. The CEIC will have the right to monitor the development of the study.

The Executive Hospital's Departments of the involved centres will be requested to declare its conformity with the participation in this study.

The project will also be sent for evaluation to the pertinent Autonomous Community Authorities and to the "Associación Española de Medicamentos y Productos Sanitarios (AEMPS)" to receive its authorization. After its consent, an application for a registry number to the "European Union Drug Regulating Authorities Clinical Trials" (EudraCT) will be also proposed.

8.3. Legal aspects

The authors of the study declare that this research has been dictated respecting the biomedical research regulation described in "Ley 14/2007, de 3 de julio, de Investigación Biomèdica" for invasive procedures.

8.4. Autonomy, privacy and confidentiality

All participants will be appropriately informed and will be given an information sheet (Annex 5) about the study prior to its inclusion, where it is reported the complete information about the trial, such as the participating centres, aiming, methodology and potential benefits and risks. Subjects will have to voluntarily sign the informed consent (Annex 5) to participate in the study.

To guarantee and protect confidentiality of all participants, the processing of all the personal information collected during the course of this trial will be performed according to "Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)". Data will be analysed ensuring the preservation of anonymity of participants.

Participants will have the right to access, modify, oppose or remove their personal data contained in the file as well as to leave the study at any time.

8.5. Safety concerns

Safety of rTMS stimulation

The rTMS stimulation protocol, including stimulation parameters and coil-positioning will follow the FDA "Special Controls Guidance Document (58)" and the safety guidelines for rTMS from "NIH Consensus Conference" on 1996 (102) and 2009 (35), (Annex 4). OFC stimulation is assumed to be well-tolerated (50,103,104) and there are no reports of ocular or visual-related side effects according to literature when targeting this area (103). Only one single case-report of retinal tear has been described after rTMS on the right DLPFC, but its correlation to stimulation technique was disesteemed due lack of casualty evidence (62).

Risk-benefit ratio

The potential benefit of the study is largely superior to rTMS risks. As said before, following the safety guidelines, rTMS is considered a safe and well-tolerated therapy. bvFTD patients do not have any other therapeutic choices to improve empathy and, according to literature review, the likelihood of clinical enhancement by rTMS is promising.

Use of sham-stimulation

It is acceptable the use of sham-stimulation ("placebo" stimulation) as no approved standard intervention to enhance empathy exists, neither any efficient treatment to stop the progression of the disease. Sham-stimulation does not produce any additional mild nor sever risks for the patients and it is reported in literature to be completely safe.

Insurance policy

To ensure the participants safety during the study it will be hired an insurance.

8.6. Post-trial provisions

In advance of the clinical trial results, the investigators will provide post-trial access to the intervention (20 sessions per year) in case the study identifies a large beneficial effect.

8.7. Transparency

External monitoring

Three independent externals agencies will take part on some processes of this clinical trial, to externally monitor it. They will ensure a correct randomization, blinding, patients' coding, collection and processing of the data, statistical analysis, safety and other aspects of the study.

Conflict of interest disclosure

All the investigators will have to declare no conflicts of interest. The authors declare that the ultimate goal of this research is to develop generalizable knowledge to improve human health and quality of life.

9. STUDY LIMITATIONS

Several limitations should be acknowledged:

- As this study is using a non-probabilistic sampling method, the subjects of the study population do not have the same chance to be elected to constitute the sample. Although this fact, the consecutive method is one of the non-probabilistic methods that induces less bias, as theoretically guarantees a free-of-choices selection. Even so, it could be possible that professionals responsible of participants recruitment do not purpose the study at every potential candidate, generating a selection bias.
- RMET and FxP require a cognitive level enough to understand the tests and correctly perform them. For that reason, patients with a CDR 2 or 3 score are excluded of this trial. That fact limits the study population to only early stages, which makes our sample not completely representative of the total bvFTD population. We have to assume this limitation to avoid introducing data collection errors in results from tests. If results are positive, further studies with late stages bvFTD population should be performed, basing their outcomes on other variables such as caregiver's reports.
- The impossibility to perform a sham stimulation without the neurophysiologist knowledge defines the trial as single-blinded. Despite this limitation, the neuro-psychologists responsible of the clinical outcome assessment will not know the result of the randomization processes, so that clinical assessment will be double-blinded.
- Previous rTMS studies lack in homogeneity regarding stimulation parameters such as number of pulses, % of MT, inter-train-interval length, number of sessions, number of trains and duration of trains. This methodological chaos reflects the lack of randomized controlled trials comparing stimulation parameters. Moreover, only one study was performed in FTD population. There is a deficient knowledge of the most appropriate and efficacy parameters. Therefore, the selected stimulation parameters used in this study could be infra-therapeutic or less effective than the ideal ones. The chosen number of sessions and number of pulses are taken from the current rTMS parameters most used to treat depression (105), which demonstrate large safety and effectiveness.
- There are few rTMS studies targeting OFC: Schutter *et al.* 2006 (104) (104), Ruffini *et al.* 2009 (50), Nauczyciel *et al.* 2014 (49) and Feffer *et al.* 2018 (103). In exception of Feffer *et al.* work, that uses AF8 and AF7 positions of 10-10 EEG system, the other ones use Fp1

and/or Fp2 positions of the 10-20 system to target OFC. According to literature, AF7 and AF8 correlate to orbital sulci and lateral orbital sulcus (80) and could be also a possible position for stimulation. This trial uses Fp1 and Fp2 because it uses a 10-20 system, a better well-known EEG comparing to 10-10, so it could be better reproduced. Further studies comparing different EEG positions are needed.

- Another limitation is the lack of experience of the neuropsychologists performing RMET, IGT and FxP. That could induce methodological mistakes and prolonged time of administration. To solve this inconvenient a mandatory training course will be imparted.
- Neurophysiologists do not have experience administrating rTMS. That could generate differences in the exact site of stimulation and device programming between different operators and intra-operators. For that reason, the attendance to rTMS training course will be mandatory.
- As the study is performed in multiples centres, differences in methodology and mistakes in data collection could be introduced. Even though this fact could be considered a limitation, it is also a strength as it gives the study an ecological validity.
- It is anticipated a patient drop-out during the trial. Patients who withdraw are more likely to have suffered adverse events and less clinical gain. That could modify and introduce a bias in the results of the statistical analysis, in favour of the efficacy and security of the technique. To solve this inconvenient, having a caregiver interested and compromised with the study is an inclusion criterion, anticipating that it could reduce the withdraw rates. To properly analyse results of patients who withdraw, a LOCF method will be used.
- Another limitation is that RMET and FxP are not currently validated for bvFTD dementia, but they both show good correlation with empathy capacities and both have been used before in bvFTD and in other pathologies. Both tests rated worst bvFTD compared to AD (30) and healthy volunteers (31).

10. CHRONOGRAM AND WORK PLAN

10.1. Participating centres

The following table shows all the participating centres:

Table 8. Participating centres and cities.

Participating Hospitals
Hospital Universitari Josep Trueta (Girona)
Hospital Clínic (Barcelona)
Hospital Vall d'Hebron (Barcelona)
Hospital Universitario de Cruces (Bilbao)
Hospital de Donostia (San Sebastián)
Hospital Universitario La Paz (Madrid)
Hospital General Universitario Gregorio Marañón (Madrid)

10.2. Research team personnel

Every participating centre will have its own multidisciplinary research team. I will be composed by minimum three neurologists (NRL1, NRL2, NR3), two neuropsychologists (NPS1, NPS2), two neurophysiologists (NPH1, NPH2) and one radiologist (R1) per centre. The principal researcher will be NRL1 of Hospital Universitari Josep Trueta (Girona) and all the other centres will appoint a head of the research team of the centre (H-NRL).

10.3. Subcontracted companies

Three external and independent companies (EXT1, EXT2, EXT3) will be subcontracted to perform the creation and maintenance of the shared database and the electronic questionnaire to fulfil the data, the randomization and data monitoring and the statistical analysis.

Table 9. Subcontracted services.

Subcontracted company	Service
External 1 – EXT1	Electronic questionnaire creation Shared database elaboration Database maintenance
External 2 – EXT2	Participants randomization and codification Data monitoring
External 3 – EXT3	Statistical analysis

10.4. Study stages

The study will include 5 stages as described below. The estimated duration of the hole project is 3 years extensible in case the sample recruitment time is increased.

Stage 1: Protocol approval, coordination and technical formation (5 months)

- Activity 1: Bibliography research. Conducted by NRL1. (1 month)
- Activity 2: Centres selection and proposal. Request the possible centres to participate in the study. Demand a written permission to perform the study by the executive department of each hospital. The principal researcher is responsible of this task. (1 month)
- Activity 3: Protocol elaboration. NRL1 writes the protocol. All the members of the study agree with the procedure. (2 months)
- Activity 4: Protocol approval. Evaluation, comment and approval of the protocol by CEIC, AEMPS, autonomous communities governments and EudraCT. The principal researcher is responsible of this activity. The protocol will be modified according to CEIC's advices and recommendations. (3 months)
- Activity 5: Shared database creation. Elaboration of a new electronic questionnaire and database to properly collect data and share all the results between the centres. Subcontracted external company 1 (EXT1) will perform this activity. (1 month)
- Activity 6: Head researchers meeting. Explain the project and coordinate all centres through an initial organizational meeting in Barcelona. All head researchers should attend, and the principal researcher will explain the aims of the study, the inclusion and exclusion criteria, the methodology and the data collection procedure. (1 day)
- Activity 7: Research team meeting. Prior to the start of the patient recruitment, all the research teams gather together. The head researcher explains the information provided on the head meeting and assigns the different task. The research team discusses the practical issues and adapts the original work plan to hospital's needs. (1 day)
- Activity 8: RMET, FxP and IGT training. Explanation of the method of administration of the empathy and decision-making tests by a neuropsychologist expert to all neuropsychologists of the study. 4-hour training, one day in Barcelona, one in Bilbao and one in Madrid. (3 days)
- Activity 9: rTMS training course. All neurophysiologists are receiving an 8-hours formation (4 hours theoretical and 4 hours of practice) imparted by an experimented neurophysiologist from Guttmann Institute (Badalona). It is also explained seizures and

other side effects management. Three formation sessions are performed, one in Barcelona, one in Bilbao and one in Madrid. (3 days)

Stage 2: Study conduct (24 months)

- Activity 10: Participants' recruitment. The neurologists consecutively recruit patients applying the inclusion and exclusion criteria. Sample selection can extend until the required size is achieved. (1 year)
- Activity 11: Randomization. Anonymization, codification and randomization of included participants, performed by external 2 organization (EXT2). (1 year)
- Activity 12: Data collection: Intervention and follow-up. All the research team members participate in this activity as detailed in "Data collection" section. This period starts simultaneously with participants enrolment but ends 1 year after the last participant is included. (2 years)
- Activity 13: Database maintenance. The EXT1 is responsible to review and maintain the shared database. (Once every 6 months for 2 years)
- Activity 14: Data monitoring and quality control. EXT2 is periodically evaluating the process and the consistency of the data. (Once every 3 months for 18 months)
- Activity 15: Research team's meetings. 2 meetings are planned during the study intercourse: in the middle and at the end of stage 2. The first meeting is intended to solve practical problems and check the data collection process to ensure the quality of the study. At the end of the follow-up the team discusses the preliminary results and evaluates all the process. (2 days)
- Activity 16: Head researchers meeting. The purpose is to coordinate between centres, comment the problems and evaluate the data collection process. It is planned for the end of stage 2, after the research teams' meeting. (1 day)

Stage 3: Data analysis and interpretation (3 months)

- Activity 17: Statistical analysis. Analysis of data by the subcontracted company (external 3). During stage 2 some analyses are also performed to control the progress of the study and evaluate the preliminary data. Final analysis will be carried out at the end of all the data collection. (2 months)
- Activity 18: Interpretation and discussion of the results. Evaluation, comment, interpretation and discussion of the results by the whole team of every centre. (2 month)

- Activity 19: Head researchers meeting. H-NRL put in common the discussions and interpretations. (1 day)
- Activity 20: Final report elaboration. The principal researcher together with assessment of all the heads of the centres will write a report with the relevant aspects of the study. (1 month)

Stage 4: Divulgation of the results (2 months)

- Activity 21: Publication in reviews. Writing of journal article. Application to different reviews to publish the findings. The principal research is responsible for this task. (1 month)
- Activity 22: Dissemination of the results. Attendance to a national and an international conference to present the conclusions of the study, by head researchers. (1 week once a month)

			2018					2019				2020				2021				
	ACTIVITIES	Person	Au	Se	Oc	Nv	De	Ja-Mr	Ap-Jn	Jl-Se	Oc-De	Ja-Mr	Ap-Jn	Jl-Se	Oc-De	Ja	Fe	Mr	Ap	My
STAGE 1	Bibliography research	NRL1																		
	Centres selection and proposal	NRL1																		
	Protocol elaboration	NRL1																		
	Protocol approval	NRL1																		
	Shared database creation	EXT1																		
	Head-researchers meeting	H-NRL																		
	Research teams meeting	ALL																		
	RMET, FxP and IGT training	All NPS																		
	rTMS training course	All NPH																		
STAGE 2	Participants recruitment	All NRL																		
	Randomization	EXT2																		
	Intervention and data collection	ALL																		
	Database maintenance	EXT1																		
	Data monitoring	EXT2																		
	Research teams meetings	ALL																		
	Heads of research meeting	H-NRL																		
STAGE 3	Statistical analysis	EXT3																		
	Interpretation and discussion	ALL																		
	Head researchers meeting	H-NRL																		
	Final report elaboration	H-NRL																		
STAGE 4	Publication in reviews	NRL1																		
	Results dissemination	H-NRL																		

11. FEASIBILITY

The principal researcher of this study is an experimented neurologist with a broad range of knowledge and specialized in cognitive impairment and dementias.

Hospital Josep Trueta (Girona) has years of experience participating in research projects. Together with Universitat de Girona, Institut de Diagnòstic per la Imatge (IDI), Institut Català d'Oncologia, Institut d'Atenció Primària (IAP) and Institut Català de Salut (ICS), they constitute "IdIbGi" (Institut d'Investigació Biomèdica de Girona). IdIbGi is a public research centre that pretends to structure and develop high quality biomedical and public health research, answering to health public problems.

IdIbGi has numerous ongoing research projects in different areas: cardiovascular diseases, inflammation and metabolism, neuroscience and onco-haematology. Within the neurology projects it can be found research groups on: medical imaging, cerebrovascular pathologies, neurodegeneration and neuro-inflammation and aging, disability and health. From some years now, part of the neurology department has actively participated in the IdIbGi research projects, providing enough baggage to perfectly execute and lead this study.

rTMS is a new stimulation therapy that is not still applied in the current clinical practice. Although all the participating centres dispose of an experimented neurophysiologist department, the technique is unknown for most of the personnel. To solve this inconvenient, all the neurophysiologists will receive a rTMS training course imparted by Guttmann Institute.

Apart from this technical lack of knowledge, all the participating centres are reference hospitals with experimented research teams and departments. All the centres do dispose of the necessary device to apply the stimulation and the necessary personnel to conduct the trail.

The diagnosis of the bvFTD and participants' recruitment will be performed by neurologists experimented in cognitive diseases, to ensure that selected patients do have FTD and no other cognitive impairments. The methodology of administration the empathy and decision-making tests will be trained to all neuropsychologists participating in the study.

12. BUDGET

12.1. Not-included costs

- Staff. The personnel participating in the research team will not be extra rewarded for this reason. It is considered that their motivations for joining the study should not be incentivized for any economic grounds. Researchers are rewarded by the scientific prestige and intellectual gains.
- Available materials. The hospitals already dispose of the rTMS device and the laptops to perform RMET test and IGT, so this material will not be considered in the study budget.

12.2. Included costs

Material costs

- Printing costs. Study information sheet (8 pages), informed consents (1 pages), FxP (20 pages), MMSE test (2 pages), BNT (15 pages), FAB-test (2 pages), NPI (1 page), ZBI (2 pages), TMT-A and TMT-B (2 pages) are required to be printed for each subject. RMET and IGT will be delivered digitally using PowerPoint © and a specific software, respectively. CDR (1 page) will be printed only once for centre to reduce unnecessary expenses. That totals approximately 50 pages per patient and 7 pages for CDR. The printing cost is 0.05€/page.
- Neuropsychologic tests license. FAB-test, BNT and IGT are not open licensed.
- rTMS structural costs. According to literature, the structural costs of one single rTMS session is approximately 25€ and each participant receives 20 sessions (106).
- Earplugs. For safety reasons, every participant will wear earplugs during stimulation time. The cost is 3€ per 10 units.
- Flexible rTMS arm. Available accessory consisting of a physic support arm. The operator can be hand-free and far from the coil. It is budgeted 1,000€ per unit.
- Brain MRI. Every participant is required a recent MRI to be included in the study. One brain MRI per participant (160€) will be budgeted, but it is predicted that some participants will already have a < 6 months MRI, so the total MRI expenses will be lower.

Personal costs

- rTMS trainer. The person imparting the rTMS training course will be paid 35€/hour, and he/she will perform a 10-hour course three-times.
- Neuropsychologist trainer. The person imparting the RMET and IGT training course will be paid 35€/hour, and he/she will perform a 4-hour course three-times.

Subcontracted services

- Statistical analysis. The subcontracted statistical analysis service will be paid 40€/hour, with an estimated total of 300 hours.
- Data monitorization. An external and independent company will be hired to monitor and assess the quality of data collection and statistical analysis. The budget is 24,000€.
- Database creation and maintenance. The creation of an electronic questionnaire, shared database and maintenance of this service is budgeted 30€/hour, with an estimated total of 300 hours of work.
- Insure policy. The stablished budget for this service is 6,000€. The insurance will cover all the possible damages derived from the study.

Travel expenses, allowances and meals costs

- Head researchers meetings. During the study, the head researchers of every centre and the principal researcher will meet 3 times. It is budgeted 150€ to cover travel, allowances and meal costs per person, per meeting.
- rTMS and neuropsychology training course. The researchers will receive 50€ for rTMS course attendance and 30€ for RMET and IGT course attendance, to cover the travel and meals costs during the training. Both trainers will receive 150€ per travel to cover also allowances during Bilbao and Madrid training.

Divulgation costs

- Publication fees. It is expected to publish a journal article exposing the main results. It is assumed 2,000€ for publication fees.
- National and international congress. To disseminate the results, head researchers will present the study results on congresses. It is expected to attend a national (750€ per inscription) and an international congress (2,000€ per inscription).

Table 10. Detailed costs of the study

ITEM		COST PER UNIT	NUMBER OF UNITS	SUBTOTAL
Material costs				
Printing costs	Information sheet	0.05€ / page	8 pages x 153 subjects	61.20€
	Informed consent	0.05€ / page	1 pages x 153 subjects	7.65€
	Neuropsychological tests	0.05€ / page	50 pages x 153 subjects	382.50€
	CDR test	0.05€ / page	7 pages	0.35€
Neuropsychologic tests with © copyright licence purchasing (FAB-test, BNT, IGT, TMT)		100€ / licence	4 tests	400€
Earplugs		3€ / 10 units	160 units	48€
rTMS structural costs		25€ / session	20 sessions x 153 subjects	76,500€
Flexible rTMS arm accessory		1,000€ / unit	5 units	5,000€
Brain MRI		160€ /1 MRI	1 MRI x 153 subjects	24,480€
			SUBTOTAL	**106,879.7€**
Personal costs				
rTMS trainer		35€ / hour	10 hours x 3 courses	1,050€
Neuropsychologists trainer		35€ / hour	4 hours x 3 courses	420€
			SUBTOTAL	**1,470€**
Subcontracted services				
Statistical analysis		40€ / hour	300 hours	12,000€
Data monitorization		30€ / hour	800 hours	24,000€
Database creation and maintenance		30€ / hour	300 hours	9,000€
Insurance policy		6,000€ / insurance	1 insurance	6,000€
			SUBTOTAL	**51,000€**
Travel expenses, allowances and meals costs				
Head researchers meetings		150€ / meeting / attendant	3 meetings x 7 attendants	2,250€
rTMS training	Attendants	50€ / attendant	16 attendants	800€
	Trainer	150€ / travel	2 travels	300€
RMET/FxP/IGT training	Attendants	30€ / attendant	16 attendants	480€
	Trainer	150€ / travel	2 travels	300€
			SUBTOTAL	**4,130€**
Divulgation costs				
Article publishing fees (submission fee and publication)		2,000€ / publication	1 publication	2,000€
Inscription to national congress		750 € / congress per attendant	7 inscriptions	5,250€
Inscription to international congress		1,500€ / congress per attendant	7 inscriptions	10,500€
			SUBTOTAL	**17,750€**
			TOTAL	**181,229.7€**

13. IMPACT ON THE NATIONAL HEALTH SYSTEM

As previously discussed, empathy loss is one of the core features of bvFTD patients, whom consequently behave less warmly and tenderly towards other people (25). Familiars, caregivers and friends can be hurt by bvFTD attitudes and can feel un-cared and uncomprehend, increasing their stress and burden (24). Nowadays, there are no therapies to stop bvFTD progression neither mitigate their lack of social abilities (17).

If the results obtained in this trial are relevant and its hypothesis is validated, it would be made an important step forward in the treatment of symptoms of bvFTD, not only for empathy enhancement but also in other cognitive domains and neuropsychiatric symptoms.

New studies would be required to assess rTMS capacity to improve disinhibition, executive functions deficits, compulsions, etc. but this study could be a methodological example for future research. This study will help to elucidate which intensity could be more effective and investigate the possible duration of rTMS aftereffects along a year of follow-up, and it will provide information about safety and tolerability of rTMS in dementia population.

If results are positive, rTMS could become an option for people suffering from dementia who currently does not have any other available treatments to improve their cognitive domains. Furthermore, it would help caregivers to diminish its suffering and burden as their could possibly feel much bonded to patients.

In conclusion, rTMS is an available, low-cost and easy to deliver technique that could enhance quality of life of bvFTD patients and their families.

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15. ANNEXES

15.1. Annex 1: FTD principal gene mutations

The following table shows FTD principal gene related mutations and their features.

Table 11. FTD principal gene mutations and their features, from Finger E. "Frontotemporal dementias" (2016) (17).

FTD PRINCIPAL GENE MUTATIONS				
Gene	Protein	Phenotype	Inheritance	Frequencies*
GRN	Progranulin	bvFTD > PPA, CBS	AD	5-22%
CORF72	Unknown	bvFTD	AD	7-29%
MAPT	Microtubule-associated tau protein	bvFTD > PSP, CBS	AD	5-15%
VCP	Valosin-containing protein	Multisystem proteinopathy/ IBMPFD	AD	3%
TARDBP	TDP-43	FTD	AD	2%
FUS/TLS	Fused in sarcoma protein	bvFTD	AD	1%
CHMP28	Chromatin-modifying protein 2B	bvFTD	AD	<1%

* in familial cases FTLD

15.2. Annex 2: International Consensus Criteria for behavioural variant FTD

International consensus criteria for behavioural variant FTD (FTDC)[a]

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A-F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A-C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]:
   - C.1. Frontal and/or anterior temporal atrophy on MRI or CT
   - C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

IV. Behavioural variant FTD with definite FTLD Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at post-mortem

C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD.

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioural disturbance is better accounted for by a psychiatric diagnosis

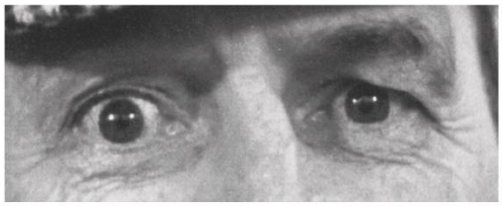
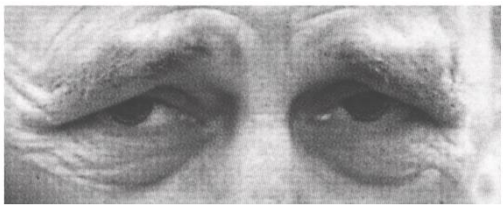
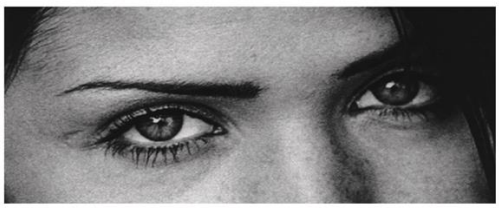
C. Biomarkers strongly indicative of AD or other neurodegenerative process

Table 12. International Consensus criteria for behavioural variant FTD (FTDC); from Rascovsky et al., "Sensitivity of revised diagnostic criteria for behavioural variant frontotemporal dementia" (2011) (21).

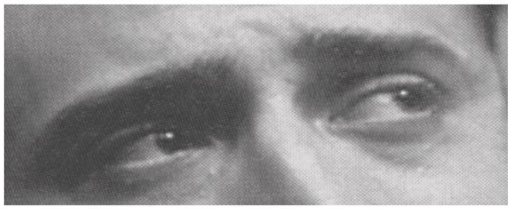
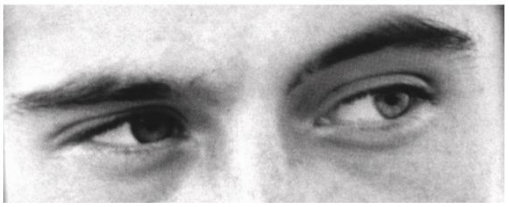
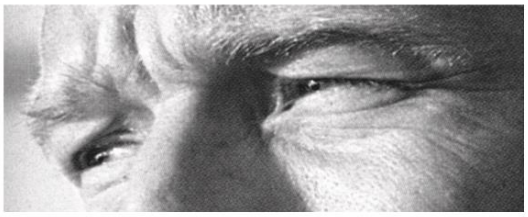
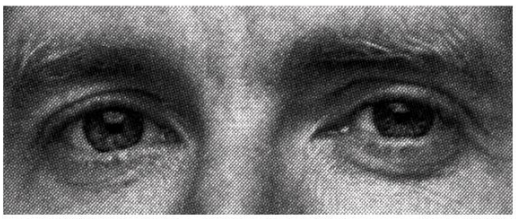
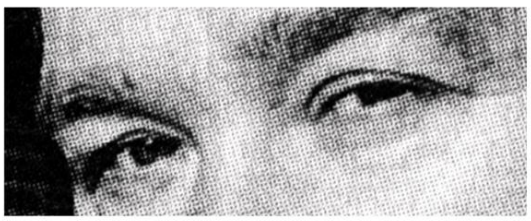
15.3. Annex 3: Spanish version of Reading mind in the eyes test (RMET)[10]

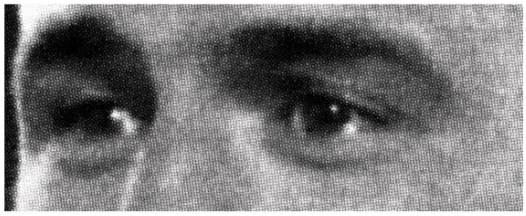
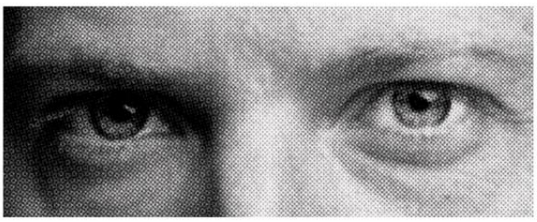
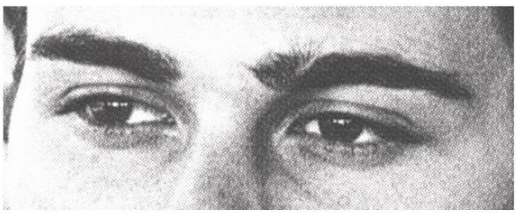
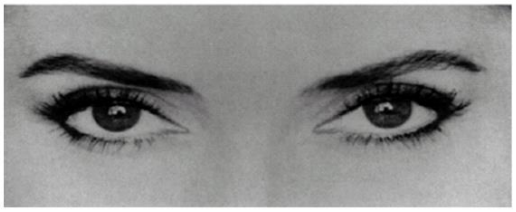
15.3.1. Photographs

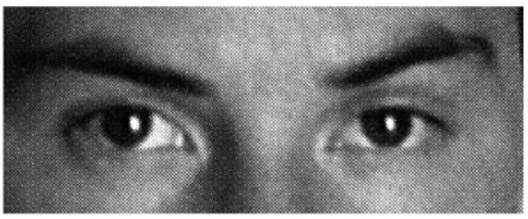
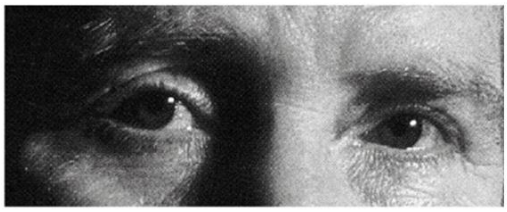
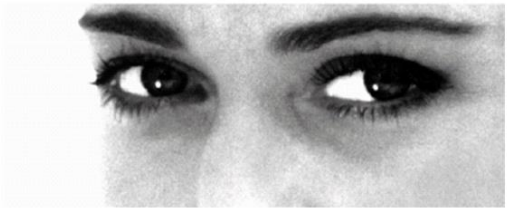
In the normal test there is one picture per page; here is only showed the images as small icons.

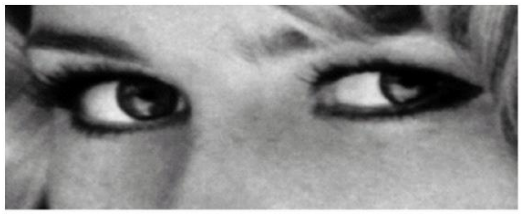
<table>
<tr><th colspan="2">Ejemplo</th></tr>
<tr><td colspan="2">CELOSO EN PÁNICO
 
ARROGANTE LLENO DE ODIO</td></tr>
<tr><th>1</th><th>2</th></tr>
<tr><td>JUGUETÓN RECONFORTANTE
 
IRRITADO ABURRIDO</td><td>ATERRORIZADO MOLESTO
 
ARROGANTE ENFADADO</td></tr>
<tr><th>3</th><th>4</th></tr>
<tr><td>BROMISTA AGOBIADA
 
DESEO CONVENCIDA</td><td>BROMISTA INSISTENTE
 
ENTRETENIDO RELAJADO</td></tr>
</table>

[10] Adapted from Baron-Cohen *et al.* (2001) (32), from Autism Research Centre (88)

5	6
IRRITADO SARCASTICO  PREOCUPADO AMISTOSO	ASUSTADA FANTASIOSA  IMPACIENTE ALARMADA
7	**8**
ARREPENTIDO AMISTOSO  INTRANQUILO DECAÍDO	ABATIDO ALIVIADO  TÍMIDO ENTUSIASMADO
9	**10**
ENFADADA HOSTIL  HORRORIZADA ANGUSTIADA	PRUDENTE INSISTENTE  ABURRIDO ASUSTADO
11	**12**
ATERRORIZADO ENTRETENIDO  ARREPENTIDO SEDUCTOR	INDIFERENTE ABOCHORNADO  ESCÉPTICO DECAÍDO

13	14
DECIDIDO EXPECTANTE  AMENAZANTE TÍMIDO	IRRITADO DECEPCIONADO  DEPRIMIDO ACUSANTE
15	**16**
ABSTRAÍDA AGOBIADA  ALENTADORA ENTRETENIDA	IRRITADO CONSIDERADO  ALENTADOR COMPASIVO
17	**18**
INSEGURA AFECTUOSA  JUGUETONA ASUSTADA	DECIDIDA ENTRETENIDA  ASUSTADA ABURRIDA
19	**20**
ARROGANTE AGRADECIDA  SARCÁSTICA VACILANTE	IMPONENTE AMISTOSO  CULPABLE HORRORIZADO

21	22
ABOCHORNADA FANTASIOSA  CONFUNDIDA EN PÁNICO	ANGUSTIADA AGRADECIDA  INSISTENTE SUPLICANTE
23	**24**
SATISFECHO ARREPENTIDO  DESAFIANTE CURIOSO	ABSTRAÍDO IRRITADO  ENTUSIASMADO HOSTIL
25	**26**
EN PÁNICO INCRÉDULA  ABATIDA INTERESADA	ALARMADO TÍMIDO  HOSTIL ANSIOSO
27	**28**
BROMISTA PRUDENTE  ARROGANTE TRANQUILIZADORA	INTERESADA BROMISTA  AFECTUOSA SATISFECHA

29	30
IMPACIENTE ASUSTADA  IRRITADA REFLEXIVA	AGRADECIDA SEDUCTORA  HOSTIL DECEPCIONADA
31	**32**
AVERGONZADA SEGURA  BROMISTA DECAIDA	SERIO AVERGONZADO  DESCONCERTADO ALARMADO
33	**34**
AVERGONZADO CULPABLE  FANTASIOSO PREOCUPADO	ASUSTADA DESCONCERTADA  RECELOSA ATERRORIZADA
35	**36**
PERPLEJA NERVIOSA  INSISTENTE PENSATIVA	AVERGONZADO NERVIOSO  DESCONFIADO INDECISO

15.3.2. Word definition handout

ABOCHORNADO/A	Avergonzado/a. *Eva se sintió muy **abochornada** por olvidar el nombre de un colega.*
ABATIDO/A	Pesimista, desconsolado/a, sin esperanza *Gerardo estaba **abatido** al no conseguir el empleo que deseaba.*
ABSTRAIDO/A	Reflexivo/a, pensativo/a, caviloso/a *Juan parecía **abstraído** en la víspera de cumplir sus 60 años.* *Susana parecía **abstraída** cuando se dirigía a encontrarse con los padres de su novio por primera vez.*
ABURRIDO/A	Que genera desgana, tedioso. *José Manuel estaba muy **aburrido** en clase.*
ACUSANTE	Echar la culpa de algo. *El policía **acusó** al hombre de robar una billetera.*
AFECTUOSO/A	Que demuestra cariño hacia alguien. *La mayoría de las madres son **afectuosas** con sus hijos, dándoles muchos besos y abrazos.*
AGOBIADO/A	Confundido/a, nervioso/a y alterado/a. *Sara se **agobió** un poco al darse cuenta de lo atrasada que iba para la reunión y de que se había olvidado un documento importante.*
AGRADECIDO/A	Sentir gratitud por algo o alguien. *Nuria estaba muy **agradecida** por la amabilidad demostrada por el extraño.*
ALARMADO/A	Temeroso/a, preocupado/a, lleno/a de ansiedad. *Clara se **alarmó** al pensar que la seguían de camino a casa.*
ALENTADOR/A	Esperanzado/a, motivador/a, contenedor/a. *Todos los padres **alentaban** a sus hijos el día de deportes en la escuela.*
ALIVIADO/A	Libre de preocupación o ansiedad *En el restaurante, Ramón se sintió **aliviado** al descubrir que no se había olvidado su billetera.*
AMENAZADOR/A	Intimidante. *El borracho corpulento actuaba de manera muy **amenazadora**.*
AMISTOSO/A	Sociable, amigable, simpático. *La **amistosa** niña dio indicaciones a los turistas sobre cómo llegar al centro de la ciudad.*
ANGUSTIADO/A	Absorto/a, enfrascado/a en los propios pensamientos, preocupado. *La preocupación por su madre hacía que Débora estuviera **angustiada** en el trabajo.*
ANSIOSO/A	Preocupado, tenso, inquieto. *La estudiante estaba **ansiosa** antes de realizar sus exámenes finales.*
ARREPENTIDO/A	Lamentarse, sentirse mal por algo. *El camarero se **arrepintió** por haber derramado la sopa sobre el cliente.* *Leo siempre se **arrepintió** de no haber viajado nunca cuando era más joven.*
ARROGANTE	Engreído/a, presumido/a, con una gran opinión de sí mismo. *El hombre **arrogante** pensaba que sabía más de política que nadie en la sala.*
ASUSTADO/A	Horrorizado/a, estupefacto/a, alarmado/a. *Juana se **asustó** al descubrir que habían entrado ladrones a su casa.*
ATERRORIZADO/A	Alarmado/a, temeroso/a. *El niño se **aterrorizó** cuando pensó que había visto un fantasma.*
AVERGONZADO/A	Sentirse abrumado/a por la vergüenza o la culpa. *El niño se sintió **avergonzado** cuando su madre lo descubrió robando dinero de su cartera.*
BROMISTA	Ser gracioso/a, chistoso/a. *Laura siempre estaba **bromeando** con la gente.*
CELOSO/A	Envidioso/a. *Antonio estaba **celoso** de los chicos más altos y más guapos de su clase.*

COMPASIVO/A	Que muestra compasión, caritativo, misericordioso. *El juez fue **compasivo** y le rebajó la pena al ladrón*
COMPRENSIVO/A	Amable, compasivo/a. *La enfermera se mostró **comprensiva** cuando le transmitió al paciente las malas noticias*.
CONFIADO/A	Seguro/a de sí mismo/a, cree en sí mismo/a. *El tenista **confiaba** mucho en ganar el partido.*
CONFUNDIDO/A	Desconcertado/a, perplejo/a. *Elisa estaba tan **confundida** por las instrucciones que le dieron que se perdió.*
CONSIDERADO/A	Respetuoso, atento, cortés. *La doctora era muy **considerada** con las personas mayores.*
CONVENCIDO/A	Certero/a, absolutamente positivo/a. Ricardo estaba convencido de que había tomado la decisión correcta.
CULPABLE	Lamentarse por hacer algo mal. Juan se sentía culpable por tener una aventura amorosa.
CURIOSO/A	Cotilla, preguntador/a, entrometido/a. Luisa tenía curiosidad por el paquete de forma rara.
DECAÍDO/A	Apesadumbrado, abatido, deprimido. Adán estaba decaído por no haber aprobado sus exámenes.
DECEPCIONADO/A	Disgustado/a, descontento/a. Los fans del Real Madrid estaban decepcionados por no haber ganado el campeonato.
DECIDIDO/A	Decisión ya tomada. Julia se veía muy decidida al entrar al centro electoral.
DECIDIENDO	Tomar una decisión. El hombre estaba decidiendo a quién votar en las elecciones.
DEPRIMIDO/A	Abatido/a. Jorge se deprimió al no recibir ninguna tarjeta de cumpleaños.
DESAFIANTE	Insolente, atrevido, no le importa lo que piensen los demás. El manifestante se mostraba desafiante aún después de haber sido enviado a prisión.
DESCONCERTADO/A	Totalmente confundido/a, perplejo/a, aturdido/a, confundido. El niño estaba desconcertado cuando visitó la gran ciudad por primera vez. Los detectives estaban completamente desconcertados por el crimen.
DESCONFIADO/A	Suspicaz, dubitativo, cauteloso. La anciana desconfiaba del extraño en su puerta.
DESEO	Pasión, apetito, anhelo. Catalina tenía un fuerte deseo por el chocolate.
DOMINANTE	Confiado/a, dominante, seguro/a de sí mismo/a. La mujer, dominante, exigió que el negocio le hiciera un reembolso.
DUDOSO/A	Dubitativo/a, con sospecha. Pedro estaba dudoso cuando le ofrecieron un televisor extremadamente barato en un bar.
EN PÁNICO	Angustiado/a, sensación de terror o ansiedad. *La familia entró **en pánico** al despertarse y encontrar la casa en llamas.*
ENFADADO /A	Irritado, contrariado. *Joaquín se **enfadó** al descubrir que había perdido el último autobús para volver a casa.*
ENTRETENIDO/A	Absorto/a, divertido/a o contento/a por algo. *Me **entretuve** mucho con el mago.* *Me **entretuve** con los chistes que contaban.*
ENTUSIASMADO/A	Sentir admiración, interés y alegría por algo. *El día de Navidad por la mañana, los niños estaban **entusiasmados** por abrir sus regalos.*
ESCÉPTICO/A	Dubitativo/a, suspicaz, receloso/a. *Jaime parecía **escéptico** cuando alguien le leía el horóscopo.*

ESPERANZADO/A	Optimista. *Carlos tenía **esperanza** en que el correo le trajera buenas noticias.*
EXPECTANTE	Esperanzado/a, a la espera de que ocurra algo. *Al comienzo del partido de fútbol, los fans estaban a la **expectativa** de un gol rápido.*
EXTRAÑADO	Apabullado/a, desconcertado/a, confundido/a. *Frank estaba **extrañado** por la desaparición de los gnomos de su jardín*
FANTASIOSO/A	Soñar despierto. *Emma **fantaseaba** con ser una estrella de cine.*
FASCINADO/A	Cautivado/a, realmente interesado/a. *En la playa, los niños estaban **fascinados** con las criaturas que encontraron entre las rocas.*
FORMAL	Con una intención seria. *Enrique era muy **formal** acerca de sus creencias religiosas.*
HORRORIZADO/A	Aterrado/a, espantado/a. *El hombre se **horrorizó** al enterarse de que su nueva esposa ya estaba casada.*
HOSTIL	Antipático/a. *Los dos vecinos se trataban con **hostilidad** tras una discusión debida a que uno de ellos ponía la música fuerte.*
IMPACIENTE	Inquieto/a, con deseos de que pase algo rápido. *Juana se **impacientaba** cada vez más mientras esperaba a su amiga que ya llevaba 20 minutos de retraso.*
IMPONENTE	Autoritario/a, mandón/a. *El sargento mayor parecía **imponente** cuando inspeccionaba a los nuevos reclutas.*
INCRÉDULO/A	Que no cree. *Simón estaba **incrédulo** al ver que había ganado la lotería.*
INDECISO/A	Inseguro/a, vacilante, incapaz de decidirse. *Tamara era tan **indecisa** que ni siquiera podía decidir qué comer.*
INDIFERENTE	Desinteresado/a, insensible, no le importa. *A Fernando le resultaba totalmente **indiferente** si iban al cine o al bar.*
INSEGURO/A	Dudoso/a, con sospecha, no cree en realidad. *María **no estaba segura** de que su hijo le estuviera diciendo la verdad.*
INSISTENTE	Demandante, persistente, perseverante. *Después de una cena de trabajo, Fran **insistió** en pagar toda la cuenta.*
INSULTANTE	Grosero/a, ofensivo/a. *Los hinchas **insultaron** al árbitro después de que pitara un penalti.*
INTERESADO/A	Preguntando, curioso/a. *Después de ver Parque Jurásico, Hugo se **interesó** mucho por los dinosaurios.*
INTRANQUILO	Preocupado/a, turbado/a, inquieto/a. *El doctor se **intranquilizó** cuando su paciente empeoró.* *Claudia se sintió un poco **intranquila** por aceptar que la llevara en coche el hombre que había conocido ese mismo día.*
INTRIGADO/A	Muy curioso/a, muy interesado/a, necesita saber más. *Una llamada telefónica misteriosa **intrigó** a Marina.*
IRRITADO/A	Exasperado/a, molesto/a. *Carmen estaba **irritada** por todo el correo basura que recibía.*
JUGUETÓN/A	Muy animado/a y divertido/a. *El pequeño Daniel estaba **juguetón** en su fiesta de cumpleaños.*
LLENO/A DE ODIO	Demostrar mucho desagrado. *Las dos hermanas se **odiaban** y siempre peleaban entre ellas.*
MOLESTO/A	Agitado/a, preocupado/a, incómodo/a. *El hombre estaba muy **molesto** cuando su madre le engañó.*
NERVIOSO/A	Apreensivo/a, tenso/a, preocupado/a. *Justo antes de su entrevista laboral, Alicia se puso muy **nerviosa**.*
OFENDIDO/A	Insultado/a, herido/a, dolido/a. *Cuando alguien hizo una broma acerca de su peso, Marta se sintió **ofendida**.*

PENSATIVO/A	Pensar sobre algo. *Felipe parecía **pensativo** días antes de cortar con su novia.*
PERPLEJO/A	Apabullado/a, confundido/a. *Juana se quedó **perpleja** al ver que su hija pequeña acababa un crucigrama en sólo cinco minutos.*
PREOCUPADO/A	Ansioso/a, impaciente, atribulado/a. *Cuando su gato se perdió, la niña estaba muy **preocupada**.*
PRUDENTE	Cuidadoso/a, precavido/a. *Sara era bastante **prudente** cuando hablaba con alguien nuevo.*
RECELOSO/A	Desconfiado, suspicaz. *La señora se mostraba **recelosa** de hacer su primera compra por internet*
RECONFORTANTE	Que brinda consuelo, que da compasión. *La enfermera **reconfortaba** al soldado herido.*
REFLEXIVO/A	Contemplativo/a, pensativo/a. *Tomás parecía **reflexivo** cuando pensaba en qué había hecho de su vida.*
RELAJADO/A	Sereno/a, calmo/a, sin preocupaciones. *En vacaciones, Patricia se sintió feliz y **relajada**.*
RESENTIDO/A	Amargo/a, hostil. *El empresario estaba **resentido** hacia su joven colega porque había sido promocionado por encima de él.*
SARCÁSTICO/A	Cínico/a, burlón/a, desdeñoso/a. *El humorista hizo un comentario **sarcástico** cuando alguien entró tarde al teatro.*
SATISFECHO/A	Contento, conforme. *Después de una buena caminata y una buena comida, David se sentía muy **satisfecho**.* Contento/a, realizado/a. *Esteban se sintió muy **satisfecho** después de haber conseguido justo el apartamento que él quería.*
SEDUCTOR/A	Pícaro, coqueto, descarado. *Sandra se mostró **seductora** cuando le guiñó el ojo a un extraño en la fiesta.*
SEGURO/A	Firme, fiable *La modelo avanzaba **segura** por la pasarela*
SERIO/A	Solemne, formal. *El gerente del banco se puso **serio** al rechazar un crédito a Miguel.*
SEVERO/A	Hosco/a, estricto/a, firme. *El maestro se veía muy **severo** cuando regañó a la clase.*
SUPLICANTE	Rogar, implorar. *Nicolás **suplicó** a su padre que le prestara el coche.*
SUSPICAZ	Que no cree, sospecha, duda. *Después de que Samuel hubiera perdido su billetera por segunda vez en el trabajo, se sintió **suspicaz** de uno de sus colegas.*
TEMEROSO/A	Aterrorizado/a, preocupado/a. *Las mujeres caminaban **temerosas** por la calle oscura.*
TÍMIDO/A	Vergonzoso, cohibido *La niña era muy **tímida** con los desconocidos*
TRANQUILIZADOR/A	Contenedor/a, alentador/a, que inspira confianza. *Andrés se mostraba **tranquilizador** al decirle a su esposa que su hijo pequeño se encontraba bien.*
VACILANTE	Indeciso/a, inseguro/a, cauteloso/a. *Andrea **vaciló** un poco antes de entrar a la sala llena de extraños.*

15.3.3. Correct answers

The solution is in **bold** and underlined.

N	Palabra 1	Palabra 2	Palabra 3	Palabra 4	*Sexo*	Puntuación
EJ	Celoso	**En pánico**	Arrogante	Lleno de odio	*H*	- (ejemplo)
1	**Juguetón**	Reconfortante	Irritado	Aburrido	*H*	
2	Aterrorizado	**Molesto**	Arrogante	Enfadado	*H*	
3	Bromista	agobiada	**Deseo**	Convencida	*M*	
4	Bromista	**Insistente**	Entretenido	Relajado	*H*	
5	Irritado	Sarcástico	**Preocupado**	amistoso	*H*	
6	Asustada	**Fantasiosa**	Impaciente	Alarmada	*M*	
7	Arrepentido	Amistoso	**Intranquilo**	Decaído	*H*	
8	**Abatido**	Aliviado	Tímido	Entusiasmado	*H*	
9	Enfadada	Hostil	horrorizada	**Angustiada**	*M*	
10	**Prudente**	Insistente	Aburrido	Asustado	*H*	
11	Aterrorizado	Entretenido	**Arrepentido**	Seductor	*H*	
12	Indiferente	Abochornado	**Escéptico**	Decaído	*H*	
13	Decidido	**Expectante**	Amenazante	Tímido	*H*	
14	Irritado	Decepcionado	Deprimido	**Acusante**	*H*	
15	**Abstraída**	Agobiada	Alentadora	Entretenida	*M*	
16	Irritado	**Considerado**	Alentador	Compasivo	*H*	
17	**Insegura**	Afectuosa	Juguetona	Asustada	*M*	
18	**Decidida**	Entretenida	Asustada	Aburrida	*M*	
19	Arrogante	Agradecida	Sarcástica	**Vacilante**	*M*	
20	Imponente	**Amistoso**	Culpable	Horrorizado	*H*	
21	Abochornada	**Fantasiosa**	Confundida	En pánico	*M*	
22	**Angustiada**	Agradecida	Insistente	Suplicante	*M*	
23	Satisfecho	Arrepentido	**Desafiante**	Curioso	*H*	
24	**Abstraído**	Irritado	Entusiasmado	Hostil	*H*	
25	En pánico	Incrédula	Abatida	**Interesada**	*M*	
26	Alarmado	Tímido	**Hostil**	Ansioso	*H*	
27	Bromista	**Prudente**	Arrogante	Tranquilizadora	*M*	
28	**Interesada**	Bromista	Afectuosa	Satisfecha	*M*	
29	Impaciente	Asustada	Irritada	**Reflexiva**	*M*	
30	Agradecida	**Seductora**	Hostil	Decepcionada	*M*	
31	Avergonzada	**Segura**	Bromista	Decaída	*M*	
32	**Serio**	Avergonzado	Desconcertado	Alarmado	*H*	
33	Abochornado	Culpable	**Fantasioso**	Preocupado	*H*	
34	Asustada	Desconcertada	**Recelosa**	aterrorizada	*M*	
35	Perpleja	**Nerviosa**	Insistente	Abstraída	*M*	
36	Avergonzado	Nervioso	**Desconfiado**	Indeciso	*H*	

15.4. Annex 4: Safety and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research

15.4.1. FDA approved parameters

The maximum Safe Train Duration Limits for avoiding seizure, described in Table 13, are the ones proposed by FDA (58) and based on articles by Wassermann (102) and Rossi (35). Above these limits, seizure risk is increased. The train duration (in seconds) is set for a specific intensity (% of the MT) level and frequency.

Table 13. FDA recommended maximum train duration for intensity and frequency. From "FDA Class II Special Control Guidelines" (58).

Maximum Safe Train Duration (seconds) Limits for Avoiding Seizure														
Freq (Hz)	**INTENSITY (% of Motor Threshold)**													
	80-100	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**
1	>1800	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

15.4.2. Safety measures

From Wassermann (102) and Rossi (35).

- Metal and electronic devices.
    - TMS is contraindicated in possession of electric/magnetic implanted devices near head/neck (≤ 30 cm) such as cochlear implants, aneurism clips, stents, ocular implants and deep brain stimulators.
    - TMS is considered safe for individuals with vagal nerve stimulator system, cardiac pacemakers, cardioverters defibrillators, pumps, intracardiac liners and spinal cord stimulators if TMS coil is not activated near these components.
    - Jewellery, glasses, watches and other potentially conducting/magnetic objects should be removed.
    - Preferentially there should be ≥ 30 cm between coil and any metal / electronic device.

- Hearing protection. Hearing protection is required during the use of rTMS devices. Patients and operators should always wear earplugs or similar with a rating of 30dB of noise reduction during rTMS treatment.
- Medication assessment. Is recommendable an accurate assessment of the concomitant drug intake during TMS as some medication increases risk of seizures.
- Staff safety. The safety of chronic exposure to electromagnetic field is unclear. It is recommended to avoid exposure closer than 40cm from the coil.
- Vulnerable populations. There is no enough evidence to recommend rTMS to pregnant patients and under 18 years-of-age population.

Side effects

TMS is a very safe and well-tolerated technique with common mild side effects and rare serious adverse effects (61).

- Common mild side effects.
    - **Local pain**: due to stimulation of superficial nerves or contracture of scalp and facial muscles. Less than 2% of participants in clinical rTMS trials discontinue the treatment due pain. It has an incidence of 40% compared to 15% in sham stimulation. Local pain rapidly vanishes after TMS and in general, improves over the course of treatment due tolerance development.
    - **Transient headache**: caused by local scalp stimulation or changes in cerebral blood flow. It can be treated with simple analgesia. It has an estimated 25% of incidence compared to 15% in sham condition groups.
    - **Neck pain**: related to prolonged uncomfortable position and immobilization during the session.
    - **Others**: toothache, paraesthesia.
- Serious adverse effects
    - **Hearing impairment**. Practically inexistent risk when hearing protection is wore.
    - **Seizures**. When following safety guidelines, the estimated overall risk of seizures is very low (< 0.1% of incidence) (41). Risk is increased in hf-rTMS, pre-existing neurological conditions, substance use and changes in concurrent medications. Longer ITIs protect from seizures. Most of reported seizures occur in pro-epileptogenic patients (family history of epilepsy, brain lesions, pro-epileptogenic

medication). All reported seizures were self-limited and occurred during the treatment session (35,41)

- **Affective switch and psychosis**. The risk of maniac/hypomanic switch appears to be low (0.84% of incidence) and mostly reported on depression or bipolar patients.
- **Vasovagal syncope**. Considered not related to therapy, otherwise as a reaction to anxiety and psycho-physical discomfort.
- **Cognitive change**. TMS can make subjects perform better or worse on a given task. Mechanisms of cognitive enhancement are not properly understood. Cumulative effects of repeated sessions of rTMS can be useful as a therapeutic tool in neurological diseases.

- Other side effects: need further research and evidence to stablish casualty.
  - **Retinal tear**. Single case report, without clear casualty relation (62).
  - **Endocrine-aftereffects**. One placebo-controlled study – Evers *et al.* 2001 – reported TSH and cortisol decrease after subthreshold stimulation rTMS.
  - **Acute changes in neurotransmitters**. Dopamine, glutamate and others.
  - **Changes in autonomic function**

15.5. Annex 5: Information sheet and informed consent[11]

FULL D'INFORMACIÓ AL PACIENT

Títol de l'estudi: *Millora de l'empatia en demència frontotemporal variant conductual a través d'estimulació magnètica transcranial repetitiva del còrtex orbitofrontal bilateral – Comparació de dos intensitats*

Investigador/a principal: _____

Centres: Hospital Universitari Josep Trueta, Hospital Clínic, Hospital Vall d'Hebron, Hospital Univesitario de Cruces , Hospital de Donostia, Hospital Universitario La Paz, Hospital General Universitario Gregorio Marañón

INTRODUCCIÓ

Ens dirigim a vostè per convidar-lo a participar, de manera completament voluntària, en un estudi que es realitzarà en persones que, com vostè, pateixen demència frontotemporal variant conductual. L'estudi ha estat aprovat pel Comitè d'Ètica i Investigació Clínica (CEIC) de l'Hospital Universitari Josep Trueta de Girona, d'acord amb la legislació vigent, i amb respecte als principis enunciats en la declaració d'Hèlsinki i a les guies de bona pràctica clínica.

La nostra intenció és que rebi la informació correcta i suficient perquè pugui avaluar i jutjar si vol o no participar-hi. Per això li preguem que llegeixi aquest full informatiu amb atenció i nosaltres li aclarirem els dubtes que li puguin sorgir. A més, podeu consultar-ho amb les persones que considereu oportú.

DESCRIPCIÓ GENERAL DE L'ESTUDI

¿Quina és la seva malaltia?

La demència frontotemporal és una malaltia neurodegenerativa poc freqüent que afecta majoritàriament a persones de 45-65 anys. La causa de la malaltia és desconeguda i provoca una alteració en la personalitat, desinhibició, falta d'empatia, problemes en la planificació, apatia i alteracions en el llenguatge, entre d'altres. És una malaltia progressiva que actualment no té cap tractament que permeti curar-la o frenar la seva evolució.

[11] Disponible també en versió castellana

¿Perquè és necessari aquest estudi?

En els darrers anys s'han produït molts estudis que investiguen els efectes de la teràpia magnètica transcranial repetitiva (rTMS) en diferents malalties: depressió, malaltia d'Alzheimer, dolor crònic, esquizofrènia, addicció al tabac, trastorn obsessiu compulsiu, trastorn per estrès post-traumàtic, afàsia post-ictus, entre d'altres; i han donat resultats prometedors. La teràpia ja s'ha aprovat a Canada, Israel i Estats Units pel tractament de persones amb depressió que no responen als medicaments clàssics. L'institut Guttmann (Badalona), entre d'altres, ja està utilitzant la rTMS per l'afàsia i la depressió.

Tot i que existeix un estudi que utilitza la rTMS en persones amb demència frontotemporal, aquest disposava de pocs pacients i, encara que els resultats semblen favorables, no són consistents. Si es pogués demostrar un benefici, podríem utilitzar aquesta tècnica pel tractament dels símptomes de persones amb demència frontotemporal.

¿Quins són els objectius de l'estudi?

L'objectiu principal d'aquest estudi és investigar si la teràpia transcranial magnètica repetitiva seria eficaç per millorar l'empatia en persones que pateixen demència frontotemporal, comparant dues intensitats d'estimulació per a valorar quina és la més eficaç.

Altres objectius plantejats són valorar si la teràpia també millora altres funcions cognitives com l'atenció, el llenguatge, les funcions executives (necessàries per una bona planificació) i la presa de decisions. També si valorarà si millora els símptomes neuropsiquiàtrics, la qualitat de vida de les persones que el cuiden. S'estudiarà si els efectes tenen continuïtat en el temps i si el grau d'atròfia inicial en la ressonància influeix en la resposta al tractament.

¿Quants centres hi participen i quant de temps dura?

Participaran 7 centres situats entre Catalunya, País Basc i Madrid, aconseguint reunir les dades d'uns 153 pacients com vostè. Està previst que la durada total de l'estudi sigui de 3 anys, però la seva participació en l'estudi serà d'1 any.

¿Quines característiques han de reunir els/les pacients per participar en l'estudi?

Els/les participants han de tenir, com vostè, un diagnòstic clar de demència frontotemporal. A més, és necessari disposar d'una persona, ja sigui un familiar o una persona propera, que convisqui amb vostè, conegui la seva malaltia i pugui informar-nos de la seva evolució.

¿En què consisteix la meva participació en l'estudi?

Per participar a l'estudi serà necessària disposar d'una ressonància magnètica recent que confirmi el diagnòstic. Si vostè disposa d'una ressonància realitzada fa menys de sis mesos, no s'haurà de repetir la prova. Si en canvi no disposa d'aquesta prova o està feta fa més d'un any, haurà de realitzar-se una nova ressonància magnètica cerebral.

Els participants, de forma totalment aleatòria, es distribuiran en tres grups de tractament: (a) tractament amb rTMS d'alta intensitat, (b) tractament amb rTMS de moderada intensitat i (c) tractament amb una falsa estimulació, com a grup control. El grup al qual vostè ha estat assignat/da no serà revelat ni a vostè ni al metge/la metgessa que li facin les avaluacions. El resultat de l'assignació només el coneixerà el/la professional que administra la rTMS.

Per portar a terme l'estudi es realitzaran les següents visites:

- Visites inicials: 2 visites per avaluar l'estat inicial de les funcions. La bateria de tests neuropsicològics per avaluar aquestes funcions, està formada per algunes proves que ja són habituals en la pràctica clínica i d'altres que són específiques per avaluar l'empatia que normalment no es realitzen. Els tests seran realitzats pel/la neuropsicòleg/a.
- Sessions de tractaments: es realitzaran 5 sessions/setmana durant dues setmanes, de dilluns a divendres. La primera sessió començarà en acabar la segona visita inicial. Les sessions tindran una durada aproximada d'1 hora i les administrarà un/a neurofisiòleg/a degudament formant en la tècnica. Al final de la segona setmana de tractament es realitzaran una altra vegada els test neuropsicològics d'empatia.
- Visites de seguiment: 4 visites, dues al cap de 6 mesos i les dues altres al cap d'un any. Es realitzaran en dies consecutius. En aquestes visites es repetiran els tests neuropsicològics de les visites inicials.

Serà necessari que **sempre** vingui acompanyat del familiar o cuidador/a, ja que en la primera visita i en les següents se li faran algunes preguntes per valorar si percep alguna millora.

¿A què em comprometo si decideixo participar en l'estudi?

Al participar en aquest estudi es compromet a assistir a les consultes que el metge li programi, i un cop acabades les sessions de tractaments, continuar amb les consecutives visites de seguiment. També es compromet a notificar qualsevol símptoma que pugui sospitar de ser un esdeveniment advers, en qualsevol moment durant estudi, encara que no tingui visita programada.

¿Tinc la possibilitat de consultar amb altres professionals?

Sempre que ho desitgi pot consultar amb altres professionals abans d'accedir a participar a l'estudi per demanar-los una segona opinió.

TRACTAMENTS ALTERNATIUS

¿Quines són les alternatives terapèutiques disponibles?

La demència frontotemporal actualment **no disposa de cap tractament** que sigui capaç de curar o aturar la progressió de la malaltia. El que sí que hi ha disponible són fàrmacs per a tractar alguns símptomes dels que provoca: neurolèptics si presenta crisis psicòtiques o conductes agressives; inhibidors selectius de la recaptació de la serotonina per l'apatia, l'agitació o irritabilitat; i es pot provar (tot i que normalment no són eficaços) fàrmacs dopaminèrgics en cas de presentar parkinsonisme. Si ho necessita, l'investigador/a responsable li pot proporcionar més informació.

¿Quin tractament rebré al finalitzar l'estudi?

En cas de que es demostri un clar benefici de la teràpia, si ho desitja podrà continuar el tractament i rebre un màxim de 20 sessions l'any, fins que s'aprovi com a teràpia.

ALTRA INFORMACIÓ RELLEVANT

Qualsevol informació nova referent a la rTMS que sigui descoberta durant la vostra participació en l'estudi, que pugui modificar la vostra disposició per participar, us la comunicarà el metge com més aviat millor.

També us volem informar de que podeu ser retirats de l'estudi en cas de que els responsables de l'estudi ho considerin oportú, ja per motius de seguretat, per qualsevol esdeveniment advers greu que es produeixi pel tractament de l'estudi o perquè considerin que no hi ha un compliment del calendari de visites i seguiment proposat. En qualsevol cas, rebreu una notificació en la qual es reflecteixi el motiu que ha ocasionat la vostra retirada.

En firmar el full de consentiment adjunt, us comprometeu a complir els procediments que se us han explicat.

BENEFICIS I RISCS DERIVATS DE LA PARTICIPACIÓ EN L'ESTUDI

¿Quins riscs assumeixo si participo en l'estudi?

Tot i que la rTMS és una tècnica segura i generalment ben tolerada, cal tenir en compte algunes qüestions de seguretat abans de sotmetre's a la teràpia, i també cal conèixer els possibles efectes indesitjats. El metge/metgessa responsable revisarà la seva història clínica i la medicació que pren habitualment per tal d'assegurar que no tingui cap motiu per ser exclòs de estudi per qüestions de seguretat.

¿Quines mesures de seguretat he de tenir en compte?

- Material metàl·lic i electrònic: la rTMS està CONTRAINDICADA en persones que tenen implants coclears o altres implants metàl·lics, elèctrics o magnètics en el cap o el coll (p.ex: clips, *stents*, estimuladors cerebrals profunds, implants oculars), ja que podria causar-ne el seu mal funcionament. Cal treure's les joies, rellotges o ulleres abans de la sessió de rTMS. Tampoc podran realitzar l'estudi persones que portin un marcapàs cardíac o altres implants cardíacs.
- Protecció auditiva: haurà de posar-se taps d'orella al realitzar la sessió de rTMS.
- Malalties de base: aquelles persones que hagin patit trastorn bipolar o algun episodi de psicosis no podran participar en l'estudi. Tampoc podran participar-hi aquelles persones que s'hagin sotmès a cirurgies cerebrals, que hagin tingut història d'epilèpsia o convulsions, que hagin patit un traumatisme cranial greu, tinguin un tumor cerebral o hagin experimentat una pèrdua auditiva relacionada amb el soroll.
- Fàrmacs: un canvi en la medicació habitual en les últimes 2 setmanes l'exclourà de l'estudi. Si pren medicació ototòxica tampoc podrà participar-hi.
- Abús de substàncies: si té dependència o habitualment consumeix substàncies com l'alcohol, cafè o altres drogues no podrà participar en l'estudi.
- Embaràs i lactància: no podrà participar en l'estudi si està embarassada o està en procés de lactància.

¿Quins efectes indesitjats pot provocar la rTMS?

- Efectes indesitjats freqüents: pot experimentar dolor transitori en la zona d'estimulació (risc alt, del 40%, però menys d'un 2% de participants abandonen el tractament per aquest motiu), mal de cap transitori, mal de coll, dolor dental i/o sensació de formigueig.

- Efectes indesitjats rars però greus: pèrdua auditiva (només en cas de no utilitzar taps), convulsions (risc < 0.1%), canvi en l'estat emocional (depressió a mania o viceversa), psicosis, síncope o canvis cognitius.
- Altres possibles efectes indesitjats, no degudament estudiats: despreniment de retina (un sol cas, en el que no es pot establir la causalitat), alteracions endocrines, alteracions en neurotransmissors.

¿Quins beneficis obtindré de la meva participació a l'estudi?

La seva participació contribuirà a un millor coneixement de la seva malaltia i a l'estudi d'un possible tractament, que podrà proporcionar futurs beneficis a les persones que la pateixin.

Al sotmetre's en aquest estudi pot ser que obtingui millores en els seus símptomes propis de la demència que pateix. També ha de conèixer que és possible que no obtingui cap benefici per la seva salut per participar en aquest estudi.

ASSEGURANÇA

L'investigador principal de l'estudi ha contractat una pòlissa d'assegurança _____ (*número de pòlissa)* amb la companyia _____ (*nom de la companyia*) que s'ajusta a la legislació vigent i que cobreix tots els possibles danys i perjudicis que es puguin derivar de l'estudi, de la qual vostè i els vostres familiars en són beneficiaris.

CONFIDENCIALITAT

¿Com s'assegurarà la confidencialitat de les seves dades?

Per la realització de l'estudi recollirem dades mèdiques sobre els seus antecedents i sobre la resposta i evolució de la intervenció. Només aquelles dades que estiguin relacionades amb l'estudi seran objecte de registre.

La recollida i anàlisi posterior de totes aquestes dades es realitzarà garantint estrictament la seva confidencialitat d'acord amb l'establert en el "Reglament (UE) 2016/679 del Parlament i del Consell, de 27 d'abril de 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes dades i pel qual es deroga la Directiva 95/46/CE (Reglament general de protecció de dades) (DOUE 4.5.2016)".

Les vostres dades es registraran en una base de dades informàtica, degudament identificades mitjançant un codi. Només l'investigador/a principal i col·laboradors podran correlacionar aquestes dades amb vostè i amb la vostra història clínica.

L'accés a la vostra informació personal quedarà restringit al/la metge/metgessa de l'estudi, col·laboradors, autoritats sanitàries, al Comitè d'Ètica i personal autoritzat, quan ho necessitin per comprovar les dades i els procediments de l'estudi, però sempre mantenint-ne la confidencialitat d'acord amb la legislació vigent. Per tant, la vostra identitat no es revelarà a cap persona tret de en cas d'urgència mèdica, requeriment de l'Administració sanitària o legal.

Només es transmetran a terceres persones i a altres països, amb la notificació prèvia a l'Agència Espanyola de Protecció de Dades, les dades recollides per a l'estudi que en cap cas no contenguin informació que us pugui identificar directament, com ara el nom i cognom, inicials, l'adreça, el núm. de la Seguretat Social, etc. En cas que es produeixi aquesta cessió, serà per a les mateixes finalitats de l'estudi descrit i garantint-ne la confidencialitat.

PARTICIPACIÓ VOLUNTÀRIA

¿Què passa si decideixo abandonar l'estudi?

Heu de saber que la vostra participació en aquest estudi és voluntària i que podeu decidir no participar-hi o canviar la vostra decisió i retirar el consentiment i abandonar l'estudi en qualsevol moment, sense donar cap tipus d'explicació.

Si decidiu retirar el consentiment per participar en aquest estudi, no s'afegirà cap dada nova a la base de dades i podeu exigir la destrucció de totes les proves identificables prèviament retingudes per evitar la realització de noves anàlisis, si bé els responsables de l'estudi poden continuar utilitzant la informació recollida sobre vostè fins aquell moment, tret que us hi oposeu expressament.

Per suposat, encara que vostè abandoni l'estudi seguirà rebent la mateixa atenció sanitària per part dels seus metges.

DUBTES I AGRAÏMENT

¿Amb qui he de contactar davant qualsevol dubte o problema que sorgeixi?

En cas de necessitar informació o comunicar qualsevol esdeveniment que succeeixi durant la realització de l'estudi, podrà posar-se en contacte amb el Dr/a. : _____, a través del número de telèfon _____ o correu electrònic _____.

Sigui quina sigui la vostra decisió, l'equip investigador vol agrair-vos el vostre tems i la vostra atenció.

Signatura del/a pacient	Signatura de l'investigador/a
Nom:	Nom:
Data:	Data:

FULL DE CONSENTIMENT INFORMAT DEL/LA PACIENT

Títol de l'estudi: *Millora de l'empatia en demència frontotemporal variant conductual a través d'estimulació magnètica transcranial repetitiva del còrtex orbitofrontal bilateral – Comparació de dos intensitats*

Jo, _____ (nom i cognoms), declaro:

- Haver llegit i entès el full d'informació que se m'ha lliurat
- Haver pogut fer les preguntes que m'hagin sorgit sobre l'assaig i haver-les resolt
- Haver rebut informació suficient sobre l'estudi
- Haver entès el meu paper com a participant en l'estudi

Declaro també haver entès que la meva participació és voluntària i que puc retirar-me de l'assaig:

- Quan vulgui
- Sense haver de donar explicacions
- Sense que això repercuteixi en les meves cures mèdiques

De conformitat amb el que estableix el Reglament (UE) 2016/679 del Parlament i del Consell, de 27 d'abril de 2016, relatiu a la protecció de les persones físiques pel que fa al tractament de dades personals i a la lliure circulació d'aquestes dades i pel qual es deroga la Directiva 95/46/CE (Reglament general de protecció de dades) (DOUE 4.5.2016), declaro haver estat informat de:

- L'existència d'una base de dades on s'inclouran les meves dades de caràcter personal
- De la finalitat de la seva recollida i dels destinataris de la informació
- Del procés de codificació de les dades
- De la disponibilitat d'exercir els drets d'accés rectificació, cancel·lació i oposició dirigint-me per escrit al titular de la base de dades

I consenteixo que les dades clíniques referents a la meva malaltia siguin emmagatzemades en un fitxer automatitzat, la informació del qual podrà ésser utilitzada exclusivament per finalitats científiques.

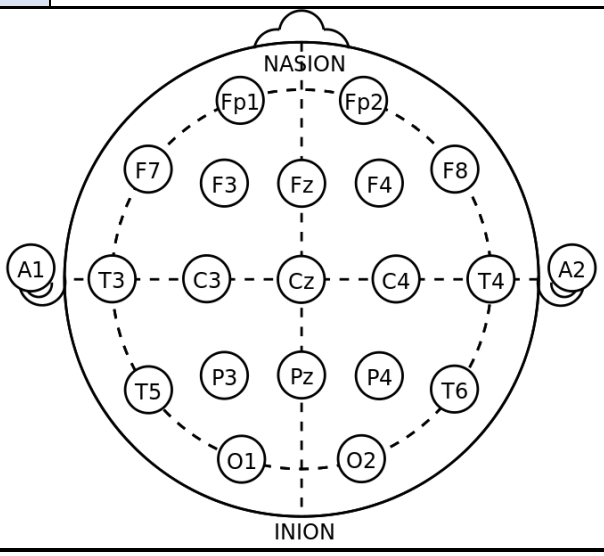
Dono lliurement la meva conformitat per participar en l'assaig.

Data:_____ Signatura: _____

15.6. Annex 6: EEG positions placement procedure

To correctly determinate the positions of Fp1 and Fp2, it must be followed the next steps:

Table 14. EEG electrode placement procedure. From: "EEG 10-20 position manual" (107)

STEPS AND PROCEDURE			
1	Take a measuring tape and use the centimetre. Measure the centre line of the scalp, from Nasion (bridge of the nose) to the Inion (occipital protuberance). Note the total length.	12	Measure and mark 5% of the total circumference to the left and right of Oz and find **O1** and **O2**.
2	Measure and mark 50% of your total, from Nasion. This is the Cz mark.	13	Measure and mark 5% of total circumference to the left and right of Fpz and find **Fp1** and **Fp2**.
3	Measure and mark 10% up from the Nasion and 10% from the Inion. These are the preliminary mark of Fpz and Oz.	14	Measure and mark 10% down from Fp1 and Fp2; these are true marks of **F7** and **F8**.
4	Mark 20%from either the first mark of Fpz or Cz. These are Fz and Pz.	15	Measure from F7 to F8 and note the distance.
5	Measure from preauricular point to the other preauricular point. Lightly run your finger up and down just anterior to ear; the indentation above the zygomatic notch is easily identified. Open the mouth slightly makes it easier to find the exact location. Note the total length.	16	Measure and mark half of the distance between F7 and F8. At the intersection with your preliminary Fz mark is the true **Fz**.
6	Measure and mark 50% of your total. At the intersection with your previous 50% mark from Naison to the Inion is the **true Cz** mark.	17	Measure from F7 to Fz and from F8 to Fz, note the distances.
7	Measure and mark 10% up from the preauricular points; these are the preliminary marks of T3 and T4.	18	Measure and mark half of the distance between F7-Fz and F8-Fz. These are your preliminary marks for F3 and F4.
8	Measure from the first mark of T3 to Cz, and from T4 to Cz. Note the total lengths.	19	Measure and mark 20% of the Naison-Inion distance from Fp1 to F3 and from Fp2 to F4, at the intersection find true **F3** and **F4**.
9	Measure and mark 50& of the totals in step 8. These are preliminary marks of C3, C4.	20	Measure from Fp1 to O1, to obtain preliminary C3, and Fp2 to O2 for preliminary C4.
10	Draw a cross section mark on Fpz. This is your **true Fpz** mark.	21	Measure and mark half of the distance Fp1-O1 and from Fp2-O2. Where your first and second marks intersect will be true **C3** and **C4**.
11	Encircle the measuring tape across yout 10% Fpz mark and the 10% Oz mark at the back of the head. Note the total circumference of the head. Measure 50% of the total circumference from Fpz to the back, and across the section with the preliminary Oz mark is the true **Oz** mark.		

15.7. Annex 7: Faux Pas Test scoring

The scores will be reported following this schedule:

Table 15. Faux Pas scoring system. Adapted using data from Stone et al.1988 (108).

ITEM	Single score	Total points	Scoring (%)
Correct control Question Scores (questions nº7 and 8)			
a. Score on Faux Pas Stories	0-2	0-20	/20
b. Score on Control Stories (CS)	0-2	0-20	/20
Do not count responses to any questions about stories with failed control questions in any scores below			
Faux pas Detection			
c. Scores on 1st and 2nd questions of Faux Pas Stories	0-2	0-20	/20
d. Scores on 1st and 2nd * questions of Control Stories	0-2*	0-20	/20
Faux pas Detection Score $Faux\ pas\ detection\ ratio = \frac{Total\ nº\ of\ Faux\ pas/controls\ correctly\ detected\ (c+d*)}{Total\ number\ of\ correct\ control\ quesions\ (a+b)} = (0-1.0)$			
"Why" score $Why\ ratio = \frac{Total\ number\ of\ 3rd\ questions\ correctly\ answered*}{20 - nº\ of\ stories\ with\ incorrect\ control\ questions} = (0-1.0)$			
Intentions score $Intention\ ratio = \frac{Total\ number\ of\ 4th\ questions\ correctly\ answered*}{20 - nº\ of\ stories\ with\ incorrect\ control\ questions} = (0-1.0)$			
Belief score $Belief\ ratio = \frac{Total\ number\ of\ 5th\ questions\ correctly\ answered*}{20 - nº\ of\ stories\ with\ incorrect\ control\ questions} = (0-1.0)$			
Empathy score $Empathy\ ratio = \frac{Total\ number\ of\ 6th\ questions\ correctly\ answered*}{20 - nº\ of\ stories\ with\ incorrect\ control\ questions} = (0-1.0)$			
* not-answered in control stories = 1 point			

15.8. Annex 8: Degrees of brain atrophy on MRI

GCA-scale (Global Cortical Atrophy)

GCA-scale is the mean score for cortical atrophy throughout the complete cerebrum. It is best scored on FLAIR images. In some neurodegenerative disorders the atrophy is asymmetric and occurs in specific regions (109).

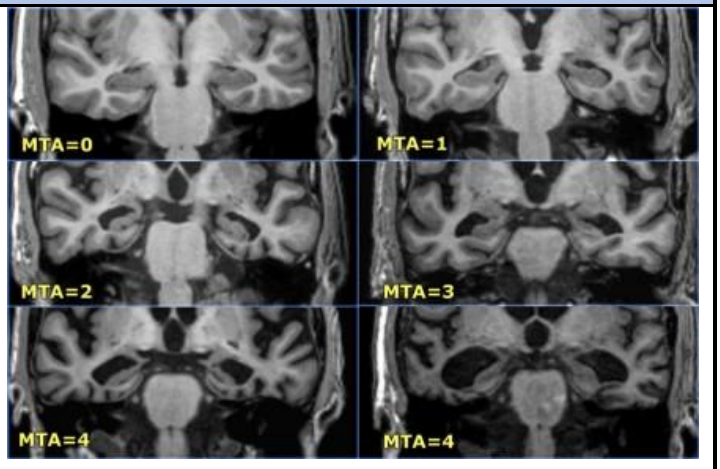
Table 16. GCA-scoring. From "Radiology Assistant"

Score	MRI Findings
0	No cortical atrophy
1	Mild atrophy: opening of sulci
2	Moderate atrophy: volume loss of gyri
3	Severe (end-stage) atrophy: "knife blade" atrophy

MTA-scale (Medial Temporal lobe Atrophy)

The MTA-score should be rated on coronal T1-weighted images at a consistent slice position. Select a slice through the corpus of the hippocampus, at the level of the anterior pons. It has a sensitivity and specificity of 85% in AD patients. The score is based on a visual rating of the width of the choroid fissure, the width of the temporal horn, and the height of hippocampal formation.

Table 17. MTA-scoring and MRI findings, adapted from "Radiology assistant" (109).

Score	MRI Findings	MRI examples
0	No atrophy	
1	Only widening of choroid fissure	
2	Also widening of temporal horn of lateral ventricle	
3	Moderate loss of hippocampal volume (decrease in height)	
4	Severe volume loss of hippocampus	
> 75 years: score 3 or more is abnormal, < 75 years: score 2 or more is abnormal		