

# POLITECNICO DI TORINO

*College of Engineering*



*Master's Degree Course in Biomedical Engineering*  
MASTER'S DEGREE THESIS

***Development of a classification system for assessing apathy's  
degree in patients with behavioral variant of frontotemporal  
dementia***

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# ***ABSTRACT***

Apathy is a behavioral symptom present in many neurological and psychiatric pathologies and it's defined as a quantitative reduction of voluntary, goal-directed behaviors. Today, apathy is assessed by questionnaires administered to the patient and/or caregiver and providing score, which compared to a threshold (norms), is able to determine the degree of apathy (clinical evaluation). However, this method of evaluating apathy is biased by the subjective nature of the patient or caregiver's perspective. Most of time, the patient is unaware of his or her real disorder (anosognosia).

The objective of this thesis entitled "DEVELOPMENT OF A CLASSIFICATION SYSTEM FOR ASSESSING APATHY'S DEGREE IN PATIENTS WITH BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA" is to address the specific question concerning the limitations of the assessment of neuropsychiatric symptoms (NPS) using interviews and rating scales, carrying out an objective and quantitative assessment of apathy. This thesis contributes to the ECOCAPTURE research program, whose general objective is to improve the characterization and assessment of apathy using behavioral sensing under ecological environments.

We developed a classification system applied on a dataset composed of 12 healthy controls (HC) and 14 patients with behavioral variant of frontotemporal dementia (bvFTD). The system follows these collected data: kinematic 3D-accelerometer data, video-based behavioral data, eye-tracking glasses data, neuropsychological and MRI data, in order to identify a behavioral signature of apathy. Data were obtained from bvFTD patients and HC enrolled in the ECOCAPTURE clinical study (<https://clinicaltrials.gov/ct2/show/NCT03272230>).

In order to classify and predict the form and intensity of apathy in bvFTD subject, based on the whole dataset, we used firstly, a clustering approach and secondly, a regression approach based on MDMR (multivariate distance matrix regression).

We obtained a classification of the dataset into three different clusters, one for the healthy volunteers (HC) and two different for the bvFTD patients (FTDa, FTDb). Moreover, we demonstrated the possibility to estimate a prediction of the apathy level based on the ECOCAPTURE dataset.



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Paolo Fulcheri



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# ***ABBREVIATIONS***

- Cx Cerebral Cortex
- FrontLAB Frontal Systems: Functions and Dysfunctions
- FTD Frontotemporal Dementia
- GDB Goal Directed behavior
- HC Healthy Controls
- PFC PreFrontal Cortex
- AOI Area of Interest
- BREF Batterie Rapide d'Existence Frontale
- bvFTD Behavioral Variant of Frontotemporal Dementia
- CNRS Centre National de la Recherche Scientifique
- DAS Dimensional Apathy Scale
- EBI Eating Behavior Inventory
- ETG Eye-Tracking Glasses
- FEF Frontal Eye Field
- FP Faux pas
- HAD Hospital Anxiety and Depression scale
- ICM Institut du Cerveau et de la Moelle Épineuse
- MMSE Mini-Mental State Examination
- NPS NeuroPsychiatric Symptoms
- PI Principal Investigator
- SMI SensoMotoric Instruments
- UMRS Unité Mixte de Recherche Scientifique
- PPA primary progressive aphasia
- nfvPPA nonfluent/agrammatic variant PPA
- svPPA semantic variant PPA
- FTD-MND FTD with motor neuron disease
- PSP-S progressive supranuclear palsy syndrome
- CBS corticobasal syndrome
- DLPFC dorsolateral PFC
- VLPFC ventrolateral PFC
- OFC orbitofrontal cortex
- DMPFC dorsomedial PFC
- ACC anterior cingulate cortex
- VMPFC ventromedial PFC
- RPFC rostral PFC



# I. INTRODUCTION

## 1.1. ICM BRAIN INSTITUTE

The Brain Institute (ICM) is an international research center dedicated to research on the brain, the spinal cord and neurological diseases [1]. It is located on the site of the Pitié-Salpêtrière Hospital (Paris XIII) and is currently directed by the Professor Alexis Brice. The institute was founded in 2005 under the supervision of the National Institute of Health and Medical Research (INSERM), the Sorbonne University, the ICM Foundation and the National Centre for Scientific Research (CNRS). The ICM is a joint scientific research unit (Inserm U 1127, CNRS UMR 7225, UPMC Paris 06 University, UMR S1127, Sorbonne University).

The ICM was set up in response to the collective and particularly public authorities' awareness that neurological and psychiatric diseases such as Alzheimer's, Parkinson's or Fronto Temporal Dementia (FTD) affect 179 million people in Europe at a total cost of €800 billion per year. Research into treatments to combat these diseases is therefore a major challenge for our society, which is why it was in the public interest to build a large-scale neuroscience research center in France. The ICM houses fundamental research activities as well as clinical research activities, but also certain start-ups with strong links to translational research, which aims to promote the dissemination of the latest therapeutic innovations to the greatest number of people. One of the major challenges of the MHI is to reduce the time between research and clinical application, as the clinical investigation center attests. The latter offers researchers a platform to conduct their clinical research studies on human beings and allows patients to benefit from the latest therapeutic and diagnostic innovations.

Research at the ICM covers 4 major scientific fields:

1. Molecular Neurosciences and Neurophysiology;
2. Integrated Neurophysiology;
3. Cognitive Neurosciences;
4. Clinical Neurosciences and translational;

A set of platforms (core facilities) provide service and expertise for the entire scientific community: ICM research teams, external academic teams, incubated companies and external companies. The ICM core facilities are distributed according research fields: molecular exploration, cellular exploration, imaging, preclinical functional exploration, functional

exploration, bio-informatics and banks. Each platform is steered by an operational and a scientific manager.

The ICM brings together on its site (Figure 1) some 655 employees from various backgrounds (20% of whom are international researchers) and different educational backgrounds: doctor, engineer, biologist, psychologist, etc. This diversity of training contributes to the excellence and interdisciplinarity of ICM research [1].

Moreover, the ICM has developed a startup incubator, from 2012. The iPEPS is the Paris Brain Institute's startup incubator and the first innovation accelerator dedicated to brain diseases in France. It is dedicated to startups in MedTech, BioTech and Digital Health.



*Figure 1. The ICM Institute*

## *1.2. PRESENTATION OF THE FRONTLAB TEAM*

This thesis has been carried out in the "FrontLAB: Frontal Systems: Functions and Dysfunctions" team. The FrontLAB is led by the Professor Richard Levy. It includes 8 Principal Investigators (PI) as well as about fifteen post-doctoral students, PhD students and trainees. The main mission of the FrontLAB is to understand and to analyze the functioning of the frontal lobes. The activities of the FRONTLAB team are structured in several research programs, all focused on the anatomical and functional organization of the frontal lobes and associated networks for higher-order cognition in health and disease:

- The “**Human Cognition** program” studies the responsibility of the frontal lobes in creativity and especially their role in the generation of new ideas.

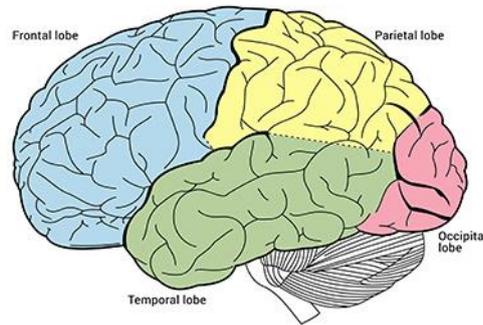
- The “**Human Behavior program**” addresses how goal-directed behavior is generated and what are the pathophysiological mechanisms underlying abnormally expressed goal-directed behaviors, in particular, disinhibition and apathy. Classical approaches are combined with the analysis of human behavior under close to real-life conditions using scenario (lab-setting) or wired tracking devices at home (natural-setting).

During my internship, I worked on the research project called ECOCAPTURE under the supervision of Bénédicte Batrancourt. My thesis is a contribute to this important project. The ECOCAPTURE project aims at defining and assessing more precisely the behavioral markers of apathy in patients with neuropsychiatric conditions. This research program is characterized by its original methodological approach using behavioral sensing under ecological conditions [2].

### *1.3. FRONTAL LOBE*

#### *1.3.1. Anatomy*

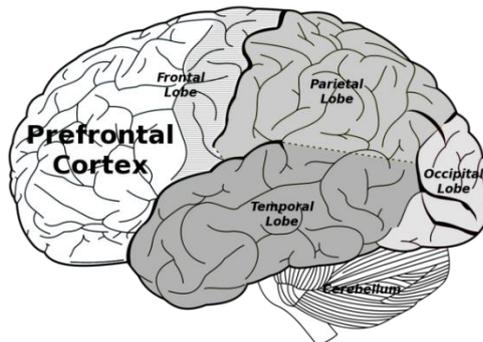
The cerebral cortex (Cx) is the outer surface of the brain, which is divided into two hemispheres (right and left). Each cerebral hemisphere can be subdivided into four lobes: 1/ Frontal lobe, 2/ Temporal lobe, 3/ Parietal lobe and 4/ Occipital lobe (Figure 2). Each lobe is associated with specific functions [3]. The frontal lobe is the part of the brain located furthest forward and is divided into 12 major areas, each linked to a specific function, including: social behavior, memory, phonology, language, hand motor skills, initiation of eye movements and semantics. Representing about 41% of the total volume of the human cerebral cortex, the frontal lobe is the largest lobe in the human brain (after it, there is the temporal lobe). Moreover, it stands out for being the area of the cerebral cortex with the largest amount of dopamine sensitive neurons, which play a decisive role on its functional capabilities.



**Figure 2.** The brain's cerebral cortex is divided into four lobes: frontal, parietal, temporal and occipital

### 1.3.2. Frontal lobe divisions

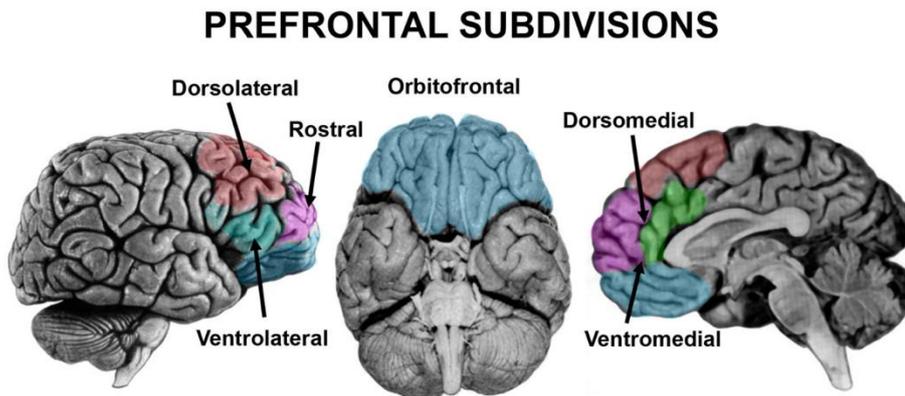
The frontal lobe can be divided into a lateral, polar, orbital (above the orbit; also called basal or ventral), and medial part. The prefrontal cortex (PFC) is the cerebral cortex which covers the front part of the frontal lobe (Figure 3).



**Figure 3.** The frontal lobe and the prefrontal cortex.

### 1.3.3. Prefrontal Cortex

The prefrontal cortex (PFC) constitutes the highest level of the cortical hierarchy dedicated to the representation and execution of actions. The consensus among diverse theoretical accounts of the organization of the PFC is that progressively more anterior PFC regions support cognitive control of progressively more abstract and temporally extended representations [5]. The PFC can be subdivided in three major regions: orbital, medial, and lateral (Figure 4) [6].



*Figure 4. Subdivisions of Prefrontal Cortex. Subdivisions of the prefrontal cortex are color-coded and labeled based upon their approximate anatomical locations in the human brain.*

#### *1.3.4. Functional areas of the Prefrontal Cortex*

The orbital and medial regions are involved in emotional behavior. The lateral region, which is maximally developed in the human, provides the cognitive support to the temporal organization of behavior, speech, and reasoning [5]. The lesion literature suggests that major divisions of the PFC control different aspects of executive function and, in turn, make different contributions to goal-directed behavior [6].

- Lesions to **dorsolateral PFC (DLPFC)** can result in deficits across a wide range of functions, including working memory, rule-learning, planning, attention, and motivation.
- Lesions of the **ventrolateral PFC (VLPFC)** cause deficits across a range of seemingly disparate functions, including spatial attention, inhibitory control, and language.
- Lesions to the **orbitofrontal cortex (OFC)** are generally associated with a loss of inhibitory and emotional control and an inability to effectively function in the social domain.
- Damage to **dorsomedial PFC (DMPFC)**, particularly the anterior cingulate cortex (ACC) has been associated with the inability to detect errors, difficulty with resolving stimulus conflict, emotional instability, inattention, and abulia or akinetic mutism.
- In contrast, **ventromedial damage (VMPFC)** disrupts social behavior as well as social, emotional, and value-based decision-making.
- **Patients with rostral PFC (RPFC)** - also referred to as the frontal pole - damage often show disorganized behavior in situations encountered in everyday life.

Overall, the lateral PFC is critical for the selection, monitoring, and manipulation of cognitive task sets; the medial PFC is critical for the updating of these task sets, and the orbital FC is critical for assigning social and emotional meaning to these task sets in order to better guide goal-directed behavior. Target-oriented behavior is in fact often seen as the result of cooperation between these prefrontal areas. The subdivision includes these four sub-regions:

1. **The lateral PFC** intervenes in the cognitive aspects of executive functions;
2. **The orbital FC** serves to contextualize behavior with regard to affective and social plans;
3. **The medial PFC** involves in the self-generation of behavior and the resolution of cognitive and affective conflicts;
4. **The RPF** is necessary for the creation and maintenance of links between temporal, spatial and semantic information.

#### *1.3.5. The Frontal syndrome*

The frontal syndrome, refers to disorders resulting from damage to the frontal lobe, and more specifically to deficits in executive cognitive functions (the ability to plan, anticipate and monitor). Frontal lesions therefore result in a certain degree of disorganization of specific instrumental activities, but above all in the possible consequences of the impairment of executive functions on elaborate behavior. This frontal syndrome is present in various neurological pathologies (Frontotemporal Dementia (FTD), stroke, Parkinson's disease, Schizophrenia, Depression, ...).

#### *1.3.6. The voluntary action*

The mechanisms and elementary processes implemented by the CPF, at the neuronal level, which constitute voluntary action can be summarized in four phases:

1. Volition, i.e. desire or need to carry out behavior directed towards a purpose;
2. Planning (in the broadest sense of term), i.e. the totality of the operations cognitive tools for developing mentally the corresponding action plan to the action to be taken ;
3. Implementation the behavioral phase, i.e. the phase of programming and execution of the response corresponding to the action plan;
4. The feedback allowing for verifying that the behavior carried out is in line with the expected one. This control phase to maintain adapted behavior or to modify it if he doesn't live up to our expectations.

## II. FRONTOTEMPORAL DEMENTIA

### 2.1. PRESENTATION AND EPIDEMIOLOGY

The term Frontotemporal Lobar Degeneration (FTLD) is used for pathological conditions that cause degeneration of frontal and temporal lobes. FTD is a heterogeneous disorder with distinct clinical phenotypes associated with multiple neuropathologic substrates. In terms of imaging, FTD is characterized in particular by atrophy of the frontal and temporal areas visible on MRI (Figure 5) [8]. FTD is a heterogeneous disorder with distinct clinical phenotypes associated with multiple neuropathological entities [7]. The term FTD encompasses clinical disorders that include changes in behavior, language, executive control and often motor symptoms.

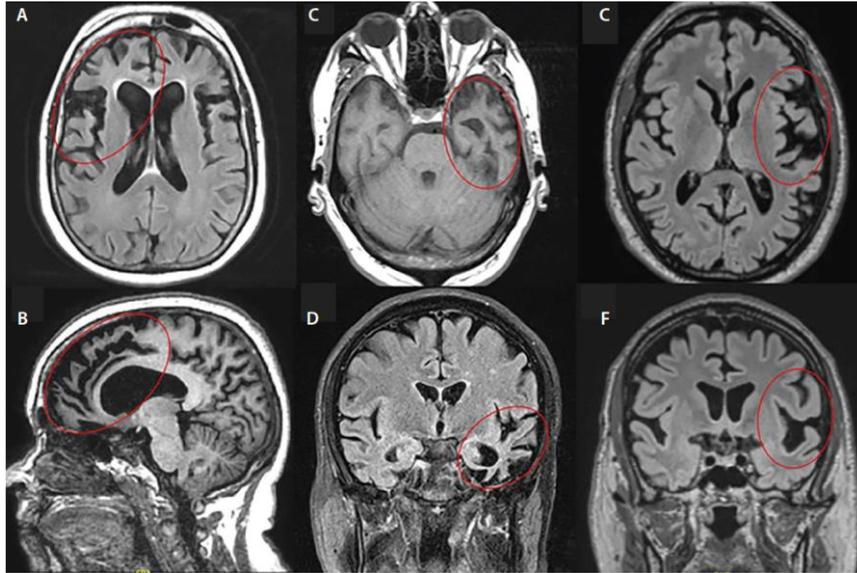
The core FTD spectrum (Figure 6) disorders include:

- behavioral variant FTD (bvFTD),
- nonfluent/agrammatic variant primary progressive aphasia (nfvPPA),
- and semantic variant PPA (svPPA).

Related FTD disorders include:

- frontotemporal dementia with motor neuron disease (FTD-MND),
- progressive supranuclear palsy syndrome (PSP-S),
- and corticobasal syndrome (CBS).

A part from the genetic factors involved in 30% of cases of FTD, the other causes of FTD are still unknown and are the subject of research programs. Among neurodegenerative dementias, FTD accounts for about 20% of cases while Parkinson's disease accounts for approximately 70% of cases. In the majority of cases, FTD occurs in patients younger than for Parkinson's disease (around 55 years of age for FTD and over 60 years of age for Parkinson's disease). The most recent epidemiological studies show that FTD is the second most frequent cause of early onset dementia, surpassed only by Alzheimer's disease (AD), with an incidence of about 20-30 cases per 100,000 inhabitants per year. FTD is a common cause of early onset dementia in patients younger than 65. The overall incidence of FTD ranges from 1 to 17 cases per 100,000 people. In individuals of more than 70 years of age, the range narrows from 1 to 4 cases per 100,000 [9].



**Figure 5.** Brain atrophy of fronto-temporal lobe in FTD subjects. Structural MRI in FTD syndromes. In bvFTD, right frontal atrophy is characteristic (A), with relative sparing of posterior structures (B). In svPPA there is left anterior temporal atrophy (C, D), whereas nfvPPA presents degeneration in the inferior frontal gyrus and adjacent structures (E, F).

## 2.2. BEHAVIORAL VARIANT OF FTD (BVFTD)

Behavioral variant FTD (bvFTD) is characterized by prominent behavioral features (e.g., apathy, loss of empathy, compulsions, and altered eating habits) and a dysexecutive neuropsychological profile [9]. BvFTD, is a good model to study apathy, as the presence of apathy is a major criterion for the clinical diagnosis of the bvFTD. The ECOCAPTURE protocol was applied in bvFTD to assess apathy [10].

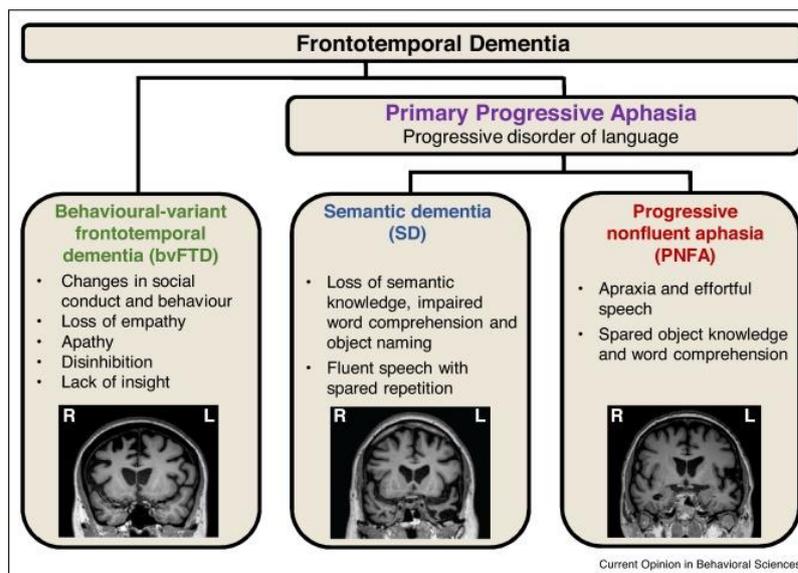


Figure 6. Different forms of Frontotemporal Dementia.

### 2.2.1 DIAGNOSIS OF BVFTD

Despite recent feeds in the bvFTD characterization, diagnosis remains a difficult challenge. It is often wrongly diagnosed with Alzheimer's disease or other forms of dementia, or psychiatric diseases. Early diagnosis of bvFTD is crucial to move towards the best therapeutic approach and the correct passage of information for family members and caregivers directly involved in the coping of the syndrome.

The final table of the International Consensus Criteria for bvFTD summarises the criteria to which the community refers scientific to diagnose bvFTD:

#### 1. Neurodegenerative disease

- a) The patient must show progressive deterioration of behavior and/or cognitive abilities, clinical observation and anamnesis

2. bvFTD possible

Three of the following behavioural/cognitive symptoms must be present for meet the criteria:

- a) Early uninhibited behaviour
- b) Early apathy or inertia
- c) Early loss of empathy
- d) Early onset of perservative, stereotypical or compulsive/ritualistic
- e) Hyperorality and dietary changes
- f) Neuropsychological profile with disexecutory syndrome, relative preservation memory and visual-space functions

3. bvFTD probable

- a) All of the following symptoms must be present to meet the criteria:
- b) Meeting the criteria for bvFTD possible
- c) Significant functional decline (detected by the stairs to the caregiver or referred by the family members)
- d) Neuroimaging consistent with FTD (i.e. frontal and/or temporal atrophy front detected by CT or MRI, or frontal hypoperfusion or hypometabolism via SPECT or PET)

4. bvFTD with definitia pathology FTL D Criteria A and Criteria B or C must be present to meet the criteria

- a) Meets the criteria for possible or probable bvFTD
- b) Histopathological evidence of FTL D
- c) Presence of a recognised genetic mutation

5. Exclusion criteria of bvFTD

Criteria A and B must be negative for each bvFTD diagnosis. Criteria C may be positive for bvFTD possible but negative for bvFTD probable;

- a) Pattern of deficits corresponds better or medical disorder
- b) Behavioral symptoms are more easily attributable to a psychiatric etiology

Biomarkers are clearly indicative of a neurodegenerative process Alzheimer's type or others.

### III. APATHY

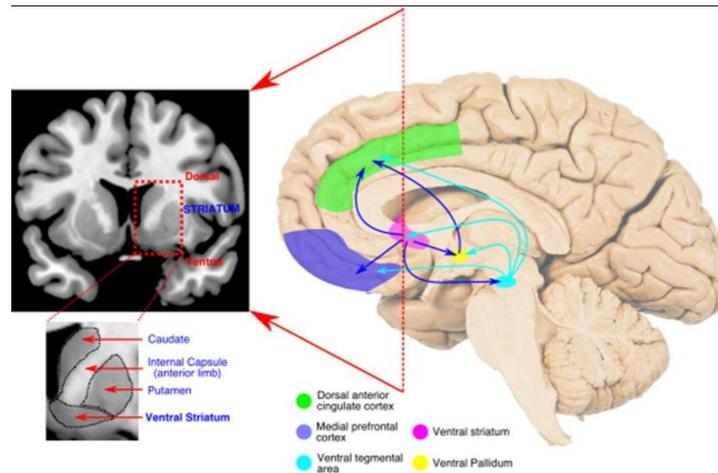
The word apathy comes from the Greek word pathos or passion, which describes a state of indifference or inertia. Over time the concept of apathy has undergone changes in meaning and remains vaguely defined and widely applied [10]. Sometimes described as a symptom of other disorders such as depression, Marin clarified the concept of apathy for medical purposes by proposing to define apathy as a lack of motivation [11]. A warning with Marin's definition is that "lack of motivation" may not be the only mechanism contributing to apathetic behavior. Others have noted that apathy is synonymous with poor initiation. Apathy can be explained and examined within the concept of goal directed behavior (GDB). Apathy has been conceptualized as deficit in GDB [12]. Currently the most widespread theoretical model concerning the neural bases involved in apathy is based on the complex neural basis model of goal-directed behavior. The ECOCAPTURE research program falls within this conceptual framework and studies apathy within the concept of GDB.

#### 3.1. MAIN COMPONENTS OF GOAL-DIRECTED BEHAVIOR

Let's assume that GDB is a multi-component process (Figure 8) [14] that includes at least three main components:

- **Initiation:** refers to the ability to self-generate or activate actions. Failure to perform behavior results in apathy when processing is unable to generate a signal significant enough to initiate a response. Difficulty with initiation has been reported in patients with focal lesions in the anterior cingulate cortex (ACC) [13].
- **Planning:** describes the ability to process execution plans. It includes high dimensional cognitive processes in the executive function that are necessary to formulate and achieve complex, multi-step objectives. The anatomical basis of executive dysfunction has been linked to dorsolateral portions of the prefrontal cortex (DLPFC).

- **Motivation:** means the ability to associate emotional signals (positive or negative) with value in the execution of particular actions. Because rewards and avoidance of negative consequences constitute basic goals of behavior, motivational functions are based partly on the processing of reward information [14]. The study of reward processing and resultant apathetic behavior in the bvFTD population offers essential insights into the functions of the orbitofrontal cortex (OFC).



*Figure 7. Complex model of the neural bases of goal-directed behavior.*

### 3.2. EVALUATION OF APATHY

The ECOCAPTURE research project is guided by the general question of the assessment and the measurement of neuropsychiatric symptoms (NPS) and the more specific question concerning the limitations of the methods employed to collect the measures due to their subjectivity. NPS assessment is crucial in clinical practice as well as in clinical research and also in future clinical trials targeting disease-modifying therapies. Validated assessment scales are now available for the majority of these symptoms. However, these scales are biased by the subjective nature of the patient or caregiver's perspective.

Apathy is usually assessed by questionnaires (e.g. Starkstein Apathy Scale) administered to the patient and/or caregiver and providing information about the patient's internal state, thoughts and past activities, globally suggesting a loss of motivation to perform daily activities. The Starkstein Apathy Scale (SAS) [15] consists of 14 questions: depending on the patient's answers to these questions, the patient is given a score that determines whether or not he or she is

apathetic. This type of diagnostic method is problematic because the answers to the questionnaire cannot be completely free of subjectivity and interpretation. In addition, patients may present anosognosia (lack of knowledge of their disorders).

Apathy Scale (Starkstein *et al.* 1995).

Questions	Not at all	Slightly	Some	A lot
1. Are you interested in learning new things?				
2. Does anything interest you?				
3. Are you concerned about your condition?				
4. Do you put much effort into things?				
5. Are you always looking for something to do?				
6. Do you have plans and goals for the future?				
7. Do you have motivation?				
8. Do you have the energy for daily activities?				
9. Does someone have to tell you what to do each day?				
10. Are you indifferent to things?				
11. Are you unconcerned with many things?				
12. Do you need a push to get started on things?				
13. Are you neither happy nor sad, just in between?				
14. Would you consider yourself apathetic?				

**Figure 8.** Starkstein Apathy Scale.

Thus, one of the major challenges of the ECOCAPTURE project is to develop a quantitative scale for assessing apathy in order to get around the lack of objectivity of current scales and thus to provide an objective assessment of the subject's level of apathy. To address the specific question concerning the limitations of the assessment of the symptoms using interviews and rating scales, and for supplementing the patient's subjective evaluation of health state, ECOCAPTURE relies on an emerging and promising research field: behavioral sensing and mobile health (mHealth) due to the rapid growth of wearable and/or wireless sensors, as well as devices smart-sensor integration in mobile phones. Behavioral sensing consists in integrating sensors into behavioral research. Recent studies, demonstrated the relevance to use new mobile technologies and wearable sensors for the assessment of the behavior in neurological conditions. Mobile technologies can provide objective and frequent measurements of disease [16]. Major of these studies have focused on the Parkinson disease (PD) to quantitatively capture movement patterns. Mobile Phone and wearable sensor have also opened the prospect of access to psychiatric disorders and symptoms. "Mobile devices allow the collection of

quantitative behavioral and functional markers in a transparent and unobtrusive way, providing an estimation of physiological and mental state” [17]. The 2018 international consensus group of experts, in the domain of apathy in brain disorders established a summary of the main instruments that can be employed to assess apathy [18]. Specifically, apathy can be assessed through:

1. a number of clinical scales and
2. new Information and Communication Technologies (ICT).

There is emerging evidence that new ICT approaches could provide clinicians with valuable additional information in terms of assessment, and therefore more accurate diagnosis of apathy [19].

## IV. THE ECOCAPTURE RESEARCH PROGRAM

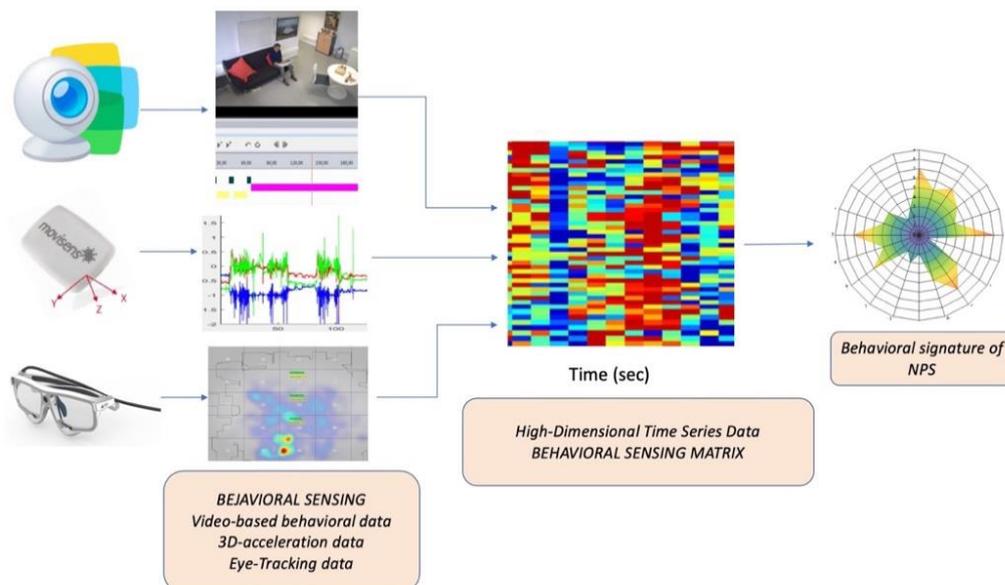
### 4.1. ECOCAPTURE PROGRAM'S OBJECTIVE AND ORGANIZATION

In order to establish the quantitative scale for assessing apathy, a research program has been set up: the ECOCAPTURE program [20]. Its primary objective is to objectively and quantitatively assess apathy in patients with FTD in its behavioral form, under ecological conditions using an integrated multimodal sensor-based system. ECOCAPTURE addresses this crucial methodological issue, which is the pathway from behavioral sensing data to behavioral signature (Figure 9). The set of video recording, kinematic and ocular data, combined with neuropsychological data, are analyzed to provide a behavioral signature of apathy and to differentiate bvFTD patients from healthy controls (HC).

The system consists of the following components:

- 6 cameras that film the patient from different angles during the entire ECOCAPTURE protocol (45 minutes)
- Video recording software (The Recorder, ®NOLDUS)
- A software for encoding patient behavior (The Observer, ®NOLDUS)
- A 3D accelerometer (MOVE II ®MOVISENS)
- A pair of eye-tracking glasses (ETG 2w, ®SMI).

The functioning of all these elements will be detailed in the presentation of the material.



**Figure 9.** The overall ECOCAPTURE method: from behavioral sensing data to behavioral signature of Neuropsychiatric Symptom (NPS).

The ECOCAPTURE research program is divided into 3 main phases:

- **Phase 1:** This first phase, called "laboratory" phase, (ECOCAPTURE@LAB) is itself subdivided into two sub-phases, each associated with a specific clinical study promoted by INSERM. The first sub-phase entitled "ECOCAPTURE PILOT" and aims to define the first metrics for distinguishing bvFTD patients from healthy volunteers and to define the study scenario. The second sub-phase, entitled "ECOCAPTURE 2", aims to highlight a behavioral signature of apathy, which will subsequently enable the development of a quantitative diagnostic tool (also known as a scale) for apathy that can be used outside the laboratory.
- **Phase 2:** The second phase concerns the clinical evaluation and home assessment (ECOCAPTURE@HOME) of the diagnostic tool developed in phase 1 with an embedded sensor system for the home phase ("apathy holter") allowing the implementation of a home telemetry program.
- **Phase 3:** Finally, the aim of the last phase is to propose a treatment of the consequences of apathy in everyday life.

This thesis focuses on the phase 1, the ECOCAPTURE@LAB and more specifically on the second sub-phase.

#### *4.1.1. Hypothesis and population*

The hypothesis of pilot phase of the ECOCAPTURE study [20] was to confirm that apathetic patients present a quantitative, objectively measurable deficit in goal-directed behavior. This pilot study should open the way, if the preliminary results were encouraging, towards a larger study to assess apathy by objective "behavioral signatures" and to link behavioral anomalies to dysfunctions of particular anatomo-functional networks. The study involved a population (n = 14) consisting of bvFTD patients (n = 7) and healthy volunteers (n = 7). The study took place at ICM's experimental psychology research platform called PRISME [21] (Figure 10). The PRISME platform is dedicated to the functional exploration of human behavior in ecological situations. The experimental paradigm was made up of two parts: the ECOCAPTURE test (observation of behavior under ecological condition) and a neuropsychological assessment for exploring the behavior and / or cognitive functions.



*Figure 10. Two bvFTD patients in the PRISME waiting room.*

#### 4.1.2. The ECOCAPTURE scenario

A short scenario taking place in a waiting room equipped with video and sensor based-system was designed to explore the underlying pathophysiological mechanisms of apathy: motivational HC. cognitive dimensions; self- HC. externally-driven goal-directed behavior (Figure 11). The scenario is made of successive phases (Guided and non-guided phases) to discriminate between participants' ability to spontaneously (self-) generate behavior in response to a given ecological environment and to organize and control their behavior in an externally-driven situation.



*Figure 11. The ECOCAPTURE scenario*

#### 4.1.3. Data acquisition

During the 45 minutes of the experimental session, data was collected with a sensor (Move II, ®MOVISENS) and a video recording (The Recorder, ®NOLDUS). Video recording is analyzed on the basis of an ethogram (coding scheme) using a software (The Observer, ®NOLDUS) in order to extract variables reflecting the duration or frequency of the behaviors. The sensor records raw three-dimensional acceleration, barometric air pressure and temperature data. From these data,

parameters such as activity rate, body position, steps, energy expenditure and metabolic equivalents are secondarily calculated using the DataAnalyzer software (®MOVISENS). The neuropsychological assessment (including the STARKSTEIN Apathy Clinical Scale) generated a set of scores that were correlated with observations in the PRISME room.

#### *4.1.4. ECOCAPTURE metrics*

The PILOT study identified a list of metrics for testing statistical discrimination between the bvFTD group and the HC group. These metrics are separated into three blocks: the NEUROSPY block (Table 1), the VIDEO block (Table 2) and the SENSOR block (Table 3). The NEUROSPY block groups together the metrics concerning the subject's results in the different neuropsychological tests. The metrics of the NEUROSPY block reflect the state preservation of mental and cognitive capacities as well as the level of apathy of the subject. These metrics are evaluated during a neuropsychological assessment which takes place outside the ECOCAPTURE experiment.

MMS	Mini-mental state: reports on the overall state of the cognitive system
STARK	STARKSTEIN Apathy Scale
DAS	Dimensional Apathy Scale
BREF	Rapid Frontal Existence Battery: Assessing Dysexecutive Syndrome
MATTIS	MATTIS Dementia Rating Scale (DRS). Diagnosis of (AD), also used for early detection of dementia, differential diagnosis between AD and other dementias, and dementia staging.
WCST	Wisconsin Card Sorting Test: assesses reasoning ability
EBI	Eating Behavior Inventory: Food Behavior Rating Scale
SEA	Mini-Social Cognition & Emotional Assessment: assesses functions emotional and affective limbic system. It allows to discriminate patients with depression, AD and FTD patients;
FP	Test of "faux pas": evaluation of the theory of mind
EMO	Emotional Capacity Assessment
HAD	Hospital Anxiety and Depression scale

*Table 1. List of metrics for the NEUROSPY block*

The VIDEO block compiles the behavioral metrics extracted from the subject's video encoding, these metrics were identified by manually annotating the subject's behavior on the basis of an ethogram (coding scheme) throughout the ECOCAPTURE protocol. The SENSOR block groups together all the sensor-based data: the raw output data from the sensor (e.g. 3D acceleration).

PHY	Average Physical Position over 3 min: average of the 3 states: AL, AS, DEB, MAR
LY	Lying down duration for 3 min (state =0)
SIT	Sitting duration for 3 min (state =1)
STD	Standing time duration for 3 min (state =2)
WLK	Walking time duration for 3 minutes (state =3)
ACT	Average activity over 3 minutes: average of the 3 states: NoACT, EXP, WithACT
NoACT	Duration without activity for 3 minutes (state =0)
EXP	Exploration time for 3 minutes (state =1)
WithACT	Apparent activity duration for 3 minutes (state =2)
FUSION	Fusion of the 2 variables by mean: Activity (AC) and Physical Position (PHY)
NBAC	Number of activities completed in 45 minutes
TA	Activity rate over 45 minutes
AttA	Attention to activities over 45 minutes
AttS	Attention to stimuli over 45 minutes

*Table 2. List of metrics for the VIDEO block*

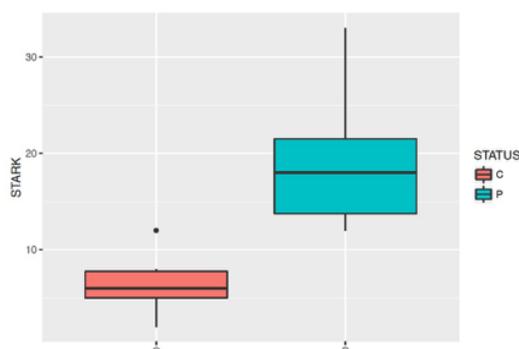
Time rel	[s]	Relative time from start of measurements in seconds
Day rel	[d]	Number of days from start of measurement
Time rel	[hh:mm:ss]	Relative time from start if measurement
Date abs	[yyyy-mm-dd]	Absolute date
Time abs	[hh:mm:ss]	Absolute time
ActivityClass	[]	Activity Class (unknown, lying, sitting/standing, slope up, jogging, slope down, walking, sitting/lying, standing, sitting/lying/standing, not worn)
Activity EnergyExpenditure	[kcal/d]	
Altitude	[m]	Altitude from barometer
BodyPosition	[]	Body position (unknown, lying supine, lying left, lying prone, lying right, upright, sitting/lying, standing, not worn)
InclinationDown	[deg]	Inclination of sensor axis down against the vertical (0 -180 °)
InclinationForward	[deg]	Inclination of sensor axis forward against the vertical (0-180 °)

InclinationRight	[deg]	Inclination of sensor axis right against the vertical (0 -180 °)
MET	[]	MET value directly calculated from regression models
Movement Acceleration	[g]	Movement Acceleration: Raw acceleration, bandpass filtered, vector magnitude
StepCount	[steps]	Count of steps per output interval
TempMean	[]	Mean temperature in output interval
TotalEnergy Expenditure	[kcal/d]	Total energy expenditure (TEE = BMR + AEE)
VerticalSpeed	[m/s]	Vertical speed, calculated from barometer
WearTimeAcc	[]	Wear time detection based on acceleration (worn, not worn)
temp	[Grad Celsius]	temp

**Table 3.** List of metrics of the SENSOR block

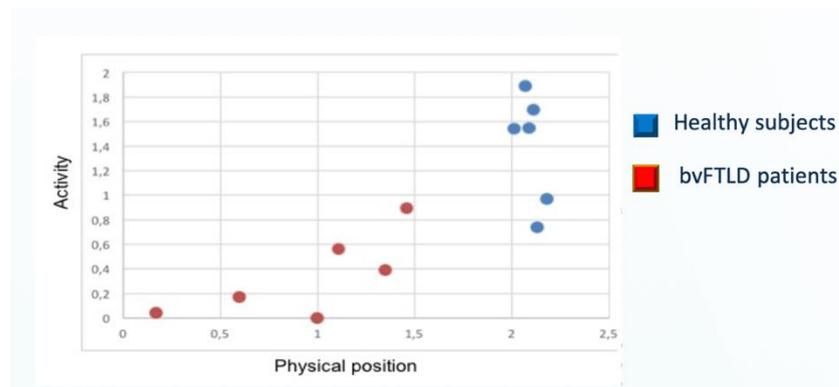
#### 4.1.5. The pilot study results

As expected, bvFTD patients were apathetic according to their score on the classical Starkstein Apathy Scale (Figure 12).



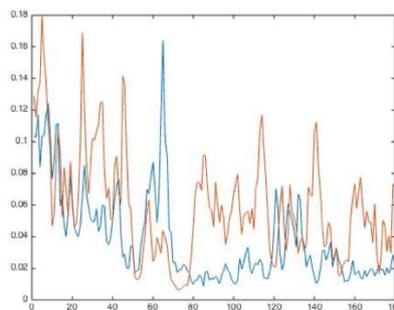
**Figure 12.** STARKSTEIN Apathy Scale.

In addition, video analysis of the first three minutes of the scenario - when the participant is alone in the room - strongly differentiates FTD patients from control subjects. Physical position (lying=0, sitting=1, standing=2, walking=3, acquired every 1 s for the first 3 min and averaged) and Activity (inactivity=0, exploration=1, activity=2, acquired every 1 s for the first 3 min and averaged) constitute discrete metrics strongly which differentiate apathetic patients from healthy participants during the first 3 minutes (Figure 13). When exposed to a new environment (ecological experimental setting), instead of interacting with it, bvFTD patients remained inactive, standing still, seating on a chair or lying on the sofa, contrasting with healthy participants who explored and interacted with this new environment.



**Figure 13.** Activity and Physical position metrics strongly differentiate apathetic patients from healthy participants.

The set of metrics in the "NEUROPSY" and "VIDEO" blocks enable discrimination between FTD patients and healthy volunteers, unlike the "SENSOR" block, which does not contain any metrics particularly able for differentiating between FTD patients and healthy volunteers. However, there was a tendency concerning the acceleration intensity signal (Figure 14) and this metric was retained for the following main study: *ECOCAPTURE 2 study*.



**Figure 14.** Acceleration intensity signal. In blue, FTD; in red, HC.

## 4.2. *ECOCAPTURE 2 STUDY*

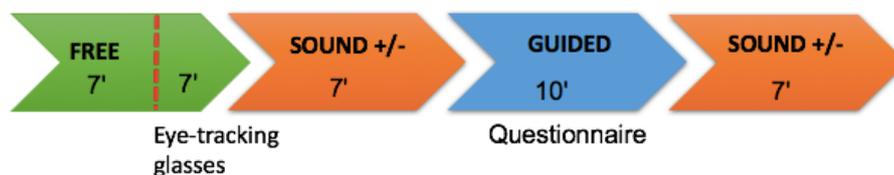
### 4.2.1. *The new ECOCAPTURE scenario*

In addition to the identification of the first metrics, the PILOTE study was also intended to freeze the ECOCAPTURE scenario, i.e. to define precisely the situations that the subjects

would encounter during the experiment. This scenario had to be the least likely in itself to generate differentiated behaviors between FTD patients and HC in order to allow the most objective comparison possible [20]. This new scenario (Figure 15) is based on the one used previously, but stimuli are better controlled concerning: 1/ Subject's preference regarding food, drinks or music; 2/ Behavior & effort-profit scale. A more controlled scenario would be able to differentiate and understand different mechanisms underlying apathy: motivation, execution, self-initiated and externally driven behavior. The entire ECOCAPTURE scenario takes place in the ICM's PRISME room. For the benefit of the ECOCAPTURE project, this room has been transformed into a waiting room according to criteria that will be described in the presentation section of the material. The overall scenario of the ECOCAPTURE protocol is a multiple-phase scenario:

- The first phase to which the subjects are exposed is a so-called "free" phase lasting a total of 14 minutes: patients are invited to visit the room at their convenience without any indication. The main of this phase is to observe self-generated behavior. Many objects used to generate interactions are present in the room: food, drink, books, magazines, board games... The last 7 minutes of the free phase are dedicated to eye-tracking: the subject wears a pair of SMI (SMI Instruments) eye-tracking glasses which capture his eye movements and the places in the room he is exploring.
- Subsequently, subjects are given a first "Sound" phase (7 minutes) to assess their degree of motivation and evaluate their behavioral response. To do this, a sound corresponding to the subject's musical tastes is emitted into the room via a loudspeaker at a low but audible volume. This sound is called positive sound. The subject is expected to move closer to the speaker to increase the sound to fully enjoy the music. As a first approach it can also be assumed that healthy volunteers will be more likely to move around to increase the sound compared to FTD patients due to their apathetic state.
- Then the subjects enter the so-called "guided" phase (10 minutes) during which they have to answer a questionnaire. This questionnaire aims to generate hetero-guided behaviors since subjects are attended to explore the room for fully filling the questionnaire. For example, they are asked to write some answers in red and so to find the red pen. It can be assumed that the subject must have the ability to maintain motivation throughout this process (GDB), which is not generally the case for apathetic patients.
- Finally, the second phase "Sound" (7 minutes) has the same aim as the first phase except that the sound is no longer positive but negative. It corresponds to an unpleasant crackling

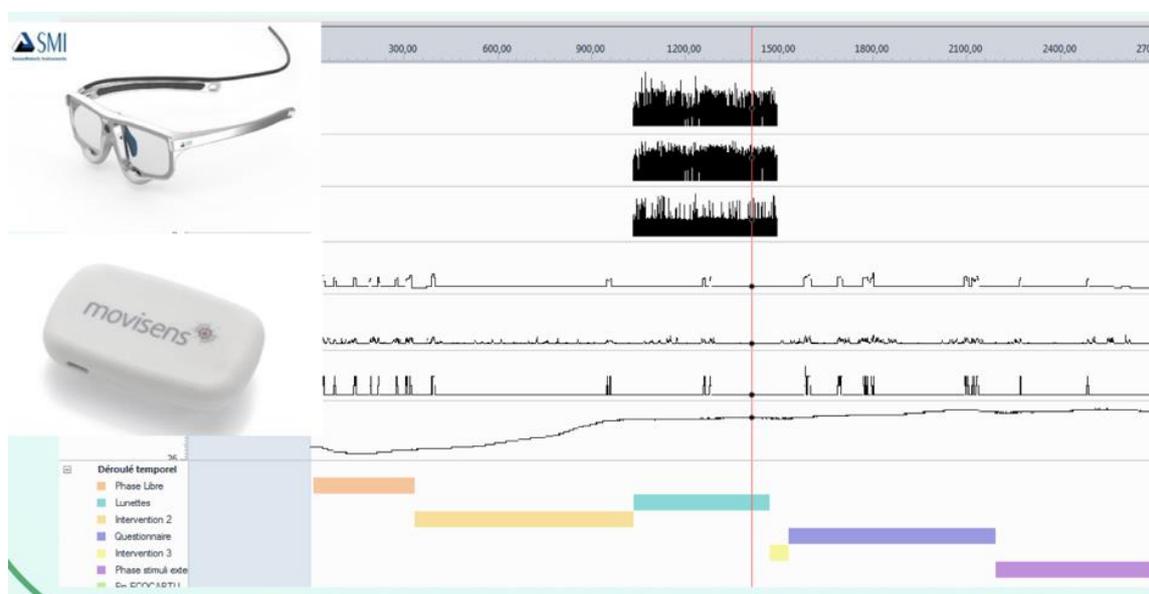
sound which rises in stages every 50 seconds for 3 minutes. The subjects are then expected to reduce the loudspeaker sound so that they are no longer audibly disturbed. As with the positive sound, it is also expected that healthy volunteers will more easily lower the loudspeaker sound than FTD patients.



**Figure 15.** The different phases of the new ECOCAPTURE scenario.

Moreover, an additional sensor was added to the system (Figure 16), with eye-tracking glasses to provide more characteristics concerning the exploration behavior.

For the entire duration of the scenario, the subject is filmed by 6 cameras and wears a mobile 3D accelerometer on his hip. Only during the last 7 minutes of the free phase, the subject wears the eye-tracking glasses. This phase will be referred to as the "eyeglass phase" in the rest of the report, while the first 7 minutes of the free phase will be referred to as the "free phase".



**Figure 16.** The overall new ECOCAPTURE system.

#### *4.2.2. Annexed activity to the ECOCAPTURE protocol*

In addition to the ECOCAPTURE protocol itself, other activities are carried out upstream or downstream of it, to ensure that subjects comply with the inclusion criteria and to assess their cognitive capacities and their level of apathy using conventional tools.

The MMS (Mini-Mental State) test and the eating behavior test (EBI) are carried out in order to check the inclusion criteria. The MMS test evaluates the subject's cognitive functions and memory capacities while the EBI index assesses the eating behavior. Following these two tests, the subject's consent is obtained.

Then, before the subject enters the PRISME room, his/her food preferences and musical tastes are assessed in order to configure the PRISME room according to his/her responses. The ECOCAPTURE protocol, lasting 45 minutes, then takes place.

Following this, a neurological assessment is carried out by subjecting the subjects to the following tests: Hayling test, mini-SEA, BREF test, HAD depression scale, etc. (see Table 1). Apathy is assessed in a "classical" way via the STARKSTEIN and DAS apathy scales. An evaluation of apathy via an experimental task is also carried out: the ICM\_APATHY\_TASKS. The subject is asked to choose behavioral tasks that he wishes to be confronted with in view of their difficulty and the gain associated with them. The greater the difficulty of the task, the greater is the associated gain.

Finally, before the subject's departure from the ICM, a debriefing of the ECOCAPTURE protocol takes place in order to collect the impressions and undesirable events that the subject may have encountered during the protocol.

#### *4.2.3. The ECOCAPTURE 2 study results*

Healthy participants and bvFTD patients were submitted to the ECOCAPTURE protocol, designed to obtain objective and quantifiable signatures of behavioral syndromes such as apathy. This study obtained formal approval from the local ethical research committee. Behavior was monitored by means of multimodal tools (video and a sensor-based acquisition system), then categorized using ethograms and statistically processed. We related here, the analyses and the results from the first article published by Batrancourt et al. concerning the ECOCAPTURE 2 study [2]. In this study, the authors focused on self-initiated behavior, i.e.,

behavior in the very first minutes of the scenario, during which participants entered the room and were encouraged to freely explore it. In-room behavior was analyzed in isolation and in correlation with selected neuropsychological tests.

They enrolled 14 patients with bvFTD (8 females and 6 males; mean age:  $(65.29 \pm 11.28)$  who were included in the study according to the international consensus criteria [22]. They were compared to a group of 14 sex- and age-matched healthy controls (HC) (7 females and 7 males; mean age:  $62.14 \pm 7.46$ ), with the same level of education. The two populations were comparable in gender and education level.

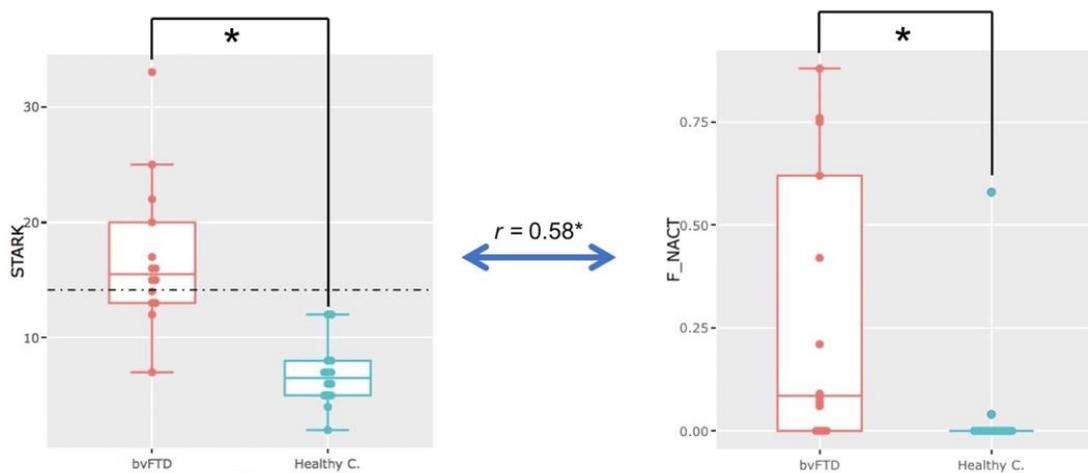
Accordingly, during the first 7 minutes that represented the freely moving (self-guided) phase, they recorded metrics that would best describe participants' behavior in the room according to their a priori hypotheses that bvFTD patients would be less active than normal participants, that their exploration would be shorter, that their total duration of non-activity would be longer and that their active behavior would be reduced. Consequently, they selected the four following metrics to describe behavior under the condition of exploration:

1. Exploration: the ratio of time spent in moving in the room or manipulating objects or remaining static but with attention oriented toward an object for more than one second and less than 10 seconds.
2. Activity: the ratio of time spent in sustained and coherent, non-automatic actions (such as manipulating objects or orienting her/his attention oriented toward an object) for more than 10 seconds. A time-out of 10 seconds is used in case of any ambiguities between the codes.
3. Non-activity: the ratio of time spent stationary (standing, seated or reclining) with no apparent ongoing activity.

The free-moving phase was analyzed as a single period of time with a total duration of 7 minutes (FULL PERIOD). To detect potential changes/switches in the dynamic of behavior during this freely moving phase, they divided it into three successive periods: the first 2 minutes (SUBPERIOD 1), when the participants entered the room and discovered it; the next 2 minutes (SUBPERIOD 2); and the last 3 minutes (SUBPERIOD 3).

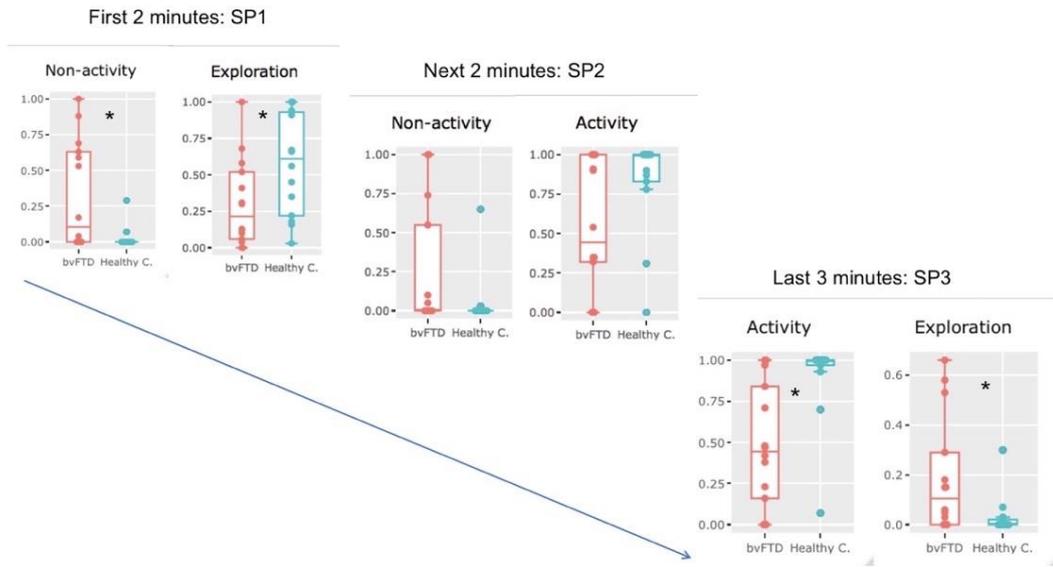
The main ECOCAPTURE 2 study results are the following [2]:

- A significant difference was observed for the Starkstein Apathy Scale (SAS) between bvFTD patients and HC. BvFTD are apathetic according SAS (Figure 17).
- In bvFTD patients, a significant part of the time spent in the room was occupied by non-activity, which was not the case for HC (Figure 18). Most of the bvFTD patients, entering in the room, went straight to a chair or to the sofa and then remained still for more than a minute. None of the HCs exhibited such behavior.
- In addition, there is a significant positive correlation between Starkstein Apathy Scale scores and the ECOCAPTURE metric non-activity for the whole population.



**Figure 17.** Starkstein and Non-Activity differentiate bvFTD and HC

- Moreover, bvFTD patients were mostly characterized by non-activity in SUBPERIOD 1 and exploration in SUBPERIOD 3, while HC were mostly characterized by exploration in SUBPERIOD 1 and activity in SUBPERIOD 3 (figure 18).



**Figure 18.** When the full period (7') was divided into three subperiods (SP1, SP2 & SP3), we observed differences in the successive behaviors adopted by HC and bvFTD patients

## V. DATASET and MATERIAL

### 5.1. RECRUITMENT CRITERIA

The recruitment criteria were defined in the INSERM ECOCAPTURE protocol [20].

#### 5.1.1. Criteria for inclusion of patients in the bvFTD group

- Diagnosis of behavioral FTD according to RascoHCky's diagnostic criteria [22].
- Preservation of understanding of instructions and ability to perform cognitive tasks.
- Integral ability to read, understand and sign the information document and informed consent (MMSE score > 20).
- Age from 40 to 85 years old.
- Absence of other brain pathology.
- Absence of psychiatric illness interfering with testing, or excessive use of psychotropic drugs, including a MADRS depression score <20.
- Informed consent to participate in the study signed.

#### 5.1.2. Criteria for inclusion of healthy control participants

- Aged from 40 to 85 years old.
- Absence of neurological or psychiatric illness interfering with the tests, or excessive consumption of psychotropic drugs.
- MMSE score > 27.
- Informed consent to participate in the study signed.

### 5.2. THE PRISME ROOM

The ECOCAPTURE behavioral tracking session of 45 minutes, takes place at the ICM "PRISME" room (Figure 19). The PRISME room is transformed into a waiting room as follows:

- Installation of a sofa, chairs, a table and a storage unit
- Availability of magazines with a theme that is appreciated by the patient, as well as books
- Provision of food and drinks

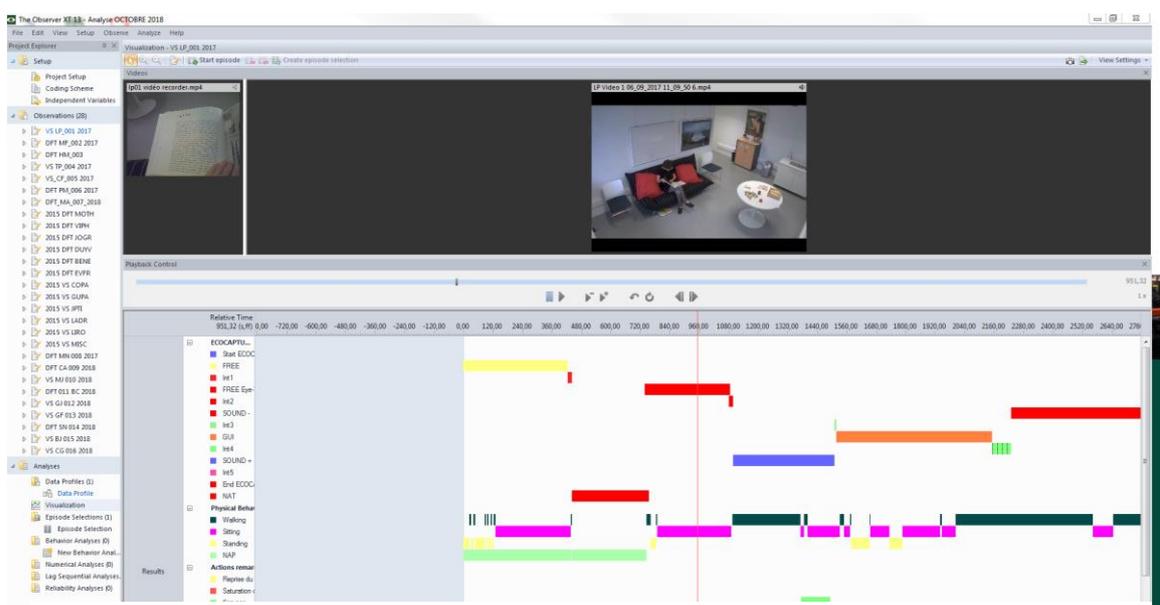
- Provision of games: Rubik's cube, puzzle, KAPLA
- Positioning of a speaker inside the room
- Putting pictures on the walls
- Provision of a kettle for making tea or coffee.



**Figure 19.** *The PRISME room.*

### 5.3. THE VIDEO CAPTURE AND ANALYSIS SYSTEM

The video capture and analysis systems are developed by the company “NOLDUS”, which is specialized in the development of innovative solutions for the analysis of animal and human behavior (ethology). The recording of the subject's behavior during the ECOCAPTURE protocol is carried out using 6 cameras positioned into the PRISME room. These 6 cameras are arranged in the room in such a way as to cover all the possible areas of exploration of the subject. They are linked to a software, called “The Recorder”, which allows to record and



**Figure 20.** *Behavioral ethogram obtained via The Observer*

visualize in real time what is captured by the 6 cameras. “The Recorder” and “The Observer” software are installed on a computer located in the control room next to the PRISME room. After recording via "The Recorder", the video analysis is performed with the software called "The Observer". This software allows to manually encode the behavior of the subject and to visualize its behavior in the form of an ethogram (Figure 20).

The ethogram is therefore a catalogue or inventory that includes all the activities and behaviors that are carried out during the ECOCAPTURE program period. For each subject it is therefore possible to instantly visualize all these behaviors for the whole duration of the experiment. In addition, the software "The Observer" allows you to merge the video data recorded by "The Recorder" with the data of the accelerometer, so that you can view the acceleration trend in parallel with the type of activity that the subject is about to perform. Thanks to this data fusion it is possible to make comparisons between the various subjects regarding the intensity of the acceleration during a given behavior and also between different behaviors. In addition, it is possible to identify the physical position and activity that causes the most energy expenditure.

#### *5.4. THE ECOCAPTURE ETHOGRAM*

The video-based behavioral metrics are generated by a manual video annotation tool, The Observer XT® (Noldus, Wageningen, The Netherlands), using an ethogram, or coding scheme, listing behavioral categories (such as exploration behavior and walking). The Observer is an observation software and a manual event recorder for the collection, management, analysis and presentation of observational data. Each record is attached to a timestamp so that the computer can produce information about the location in the timeline and the duration of any recorded behavior. The Observer translates the observations (videos) into computer language and exports an annotated csv file containing the frequency and duration of each categorized behavior, allowing the measurement of each behavior, and then processes them to produce statistics and graphs. To encode the videos, the rater visualized the six videos covering the different viewpoints of the waiting room as well as the ethogram resource.

The ECOCAPTURE ethogram is built from two main classes: “Position” and “Activity” (Table 4). These classes reflect normal and abnormal behavior expected to be observed in the waiting room. Each class was composed of mutually exclusive behaviors (i.e., categories). In regard to

the class called “Position”, we defined four categories: “reclining”, “sitting”, “standing” and “walking”. In regard to the class called “activity”, there were three categories: “exploration”, “activity” and “non-activity”.

<b>ACTIVITY</b>	Activity
	Exploration
	Non-activity
	Questionnaire oriented activity
	Questionnaire oriented exploration
	Transition
	Non-available
<b>PHYSICAL POSITION</b>	Reclining
	Sitting
	Standing
	Walking
	Non-available

*Table 4. The ECOCAPTURE Ethogram*

For each of these categories, the rater could select a “modifier” to specify the nature of the exploration (Table 5, left) or of the activity (Table 5, right). These modifiers were items present in the environment, with which the subject could interact: books, magazines, a sofa, food, drinks, and games (cf. 5.2 The PRISME room).

<b>EXPLORATION</b>	<b>ACTIVITY</b>
Books / Magazines	Cleaning
Cameras	Opening / Closing Window
Chair	Drink preparation
Cooler	Drinking
Door	Eating
Draw Unit	Playing Games
Food and Drink	Putting on/off Clothes
Furniture / Kitchen	Reading
Games / Puzzle / Kapla	Self-centered Action
Outside / Window	Space organization
Pens	Tidying
Personal Object	Writing
Phone	
Posters	
Radio / Speaker	
Room	
Scales	
Sink	
Sofa	
Table	
Without apparent objective	

*Table 5. The EXPLORATION modifiers (left) and the ACTIVITY modifiers (right).*

### 5.5. THE MOVISENS' MOVE II ACCELEROMETER

An accelerometer is a sensor capable of measuring acceleration on one, two or three axes. There are different types of accelerometers: piezoresistive, piezoelectric or capacitive. The accelerometer used in this protocol is piezoelectric. Its operation is based on the application of the second fundamental principle of dynamics:  $\sum \mathbf{F}_i = \mathbf{m} \mathbf{a}$ , with  $\sum \mathbf{F}_i$  is the sum of the external forces expressed in N,  $\mathbf{m}$  the mass in kg and  $\mathbf{a}$ , the acceleration in  $\text{m/s}^2$ . An electrical signal generated by a piezoelectric crystal is used to detect the displacement of the mass when it is subjected to compression. The crystal constitutes both the sensor and the elastic element and, when the mass is suspended on it, a difference in charge is generated between the two surfaces of the piezoelectric material. This difference in charge is converted into an electrical voltage proportional to the initial force. Thus, starting from the calculated electric voltage it is possible to trace the force and, through the second principle of dynamics, to find the value of the acceleration (value of the constant mass).

The Move II is an accelerometer developed by Movisens at an acquisition frequency of 64 Hz (Figure 21) [24]. The main technical characteristics of the Move II accelerometer are as follows:

- Three-dimensional acceleration measurement
- Environmental measuring temperatures: -20 to +60 °C
- Ambient humidity: 0 to 95% humidity
- Minimum and maximum measuring pressure: 300 and 1100 hPa
- Measuring capacity: from - to + 8 g
- Clean mass: 16.1 g



**Figure 21.** Movisens Move II mobile sensor.

Three types of raw data are recorded: three-dimensional acceleration, atmospheric pressure and body temperature. Recorded raw data is stored into a bin file. From this bin file, the "Data Analyser" software calculates a series of metrics which are listed in the table 3. As far as this thesis is concerned, not all metrics proved to be particularly significant. However, the sensor output data that appeared to be robust are the following:

- Acceleration according to x (g)
- Acceleration according to y (g)
- Acceleration according to z (g)
- Altitude (m)
- Tilt forward (°)
- Tilt backwards (°)
- The lateral inclination (°)

Throughout the duration of the protocol, the accelerometer was fixed on the right hip, as it was at this point that the measurements proved to be most robust.

## *5.6. THE SMI ETG 2W GLASSES*

In general, eye-tracking technology is used to determine the areas that have focused the user's visual attention when reading a web page or advertisement. Most often, the image that is presented to the subject is a still image over time. For the work done in this thesis, eye-tracking technology will not be used for a still image over time but for a succession of images that retrace the course of the subject's exploration during the eyewear phase. This will make it possible to assess the subject's capacity for exploration and, in addition, the areas of the PRISME room that have focused its attention.

Eye-tracking glasses (abbreviation: ETG for eye-tracking glasses) enable the visualization and recording of the subject's eye behavior, position and movements in real time. SMI's ETGs are equipped with 3 cameras (Figure 22):

- A first called "Scene Camera" which captures what the subject is looking at in first person or self-centered view.
- A second entitled "Right Eye Camera" which captures the behavior of the eyes and the eye movements of the right eye.
- A third one called " Left Eye Camera " which captures the behavior of the eyes and the eye movements of the left eye.



**Figure 22.** Position of the different cameras on the ETG 2w from SMI.

The SMI ETG 2w must be connected to a Samsung Galaxy Note 4 so that the collected visual data are saved in real time on the smartphone's recording unit (Figure 23) [25]. Real-time viewing of the scene camera recording is possible on the smartphone or on the laptop provided by SMI.



**Figure 23.** SMI ETG 2w glasses and the associated equipment.

The calibration of the glasses was performed immediately before the subjects entered the PRISME room, asking the subject to fix 3 predefined zones. Subsequently the subject was brought into the room wearing ETGs and fitted with a pouch with a smartphone connected to the ETG glasses via Bluetooth. Once the eyewear phase has been completed, the data, automatically saved on the smartphone, is sent via USB to the Begaze data processing software. The latter provides two output files: a first file called "Sample" (Table 6) containing the raw

eye tracking data and a second file called "Event" (Table 7) which lists the sequence of events of the eye during the experiment. There are 3 kind of events: the saccades (Table 7), the fixations (Table 8) and the blinks (Table 9). Both files have been used and processed afterwards for the subjects' classification.

METRIC	DESCRIPTION
Raw X (L/R)	Horizontal pupil position (in pixels)
Raw Y (L/R)	Vertical pupil position (in pixels)
Dia X (L/R)	Horizontal pupil diameter (in pixels)
Dia Y (L/R)	Vertical pupil diameter (in pixels)
Pupil Diameter (L/R)	Circular pupil diameter (in mm)
POR X (L/R/B)	Horizontal gaze position (in pixels)
POR Y (L/R/B)	Vertical gaze position (in pixels)
EPOS X (L/R)	Horizontal eye position
EPOS Y (L/R)	Vertical position of the eye
EPOS Z (L/R)	Position of the eye on the z-axis
GVEC X (L/R)	Gaze vector according to x
GVEC Y (L/R)	Gaze vector according to y
GVEC Z (L/R)	Gaze vector according to z

**Table 6.** Raw data from the SAMPLE file. (L/R) means that the data exists for the right eye and for the left eye. (L/R/B) means that the data exists for the right eye, for the left eye and in binocular vision.

Start	Start time of the saccade (in $\mu$ s)
End	End time of the saccade (in $\mu$ s)
Duration	Duration of saccade (in $\mu$ s)
Start Pos X	Start position of the saccade on x (in pixels)
Start Pos Y	Start position of the saccade on y (in pixels)
End Pos X	End position of the saccade on x (in pixels)
End Pos Y	End position of the saccade on y (in pixels)
Amplitude	Length of the saccade (in $^{\circ}$ )
Peak Speed	Maximum saccade speed (in $^{\circ}/s$ )
Peak Speed At	Location of the maximum speed in terms of amplitude
Average Speed	Average saccade speed (in $^{\circ}/s$ )
Peak Accel	Acceleration of the jerk in ( $^{\circ}/s^2$ )
Peak Decel	Maximum deceleration of the saccade in ( $^{\circ}/s^2$ )
Average Accel	Average acceleration of the saccade in ( $^{\circ}/s^2$ )

**Table 7.** Raw data from the EVENT file in the case of a saccade

Start	Fixation start time (in $\mu$ s)
End	Fixation end time (in $\mu$ s)
Duration	Total duration of fixation (in $\mu$ s)
Location X	Location on the horizontal axis of the fixture (in pixels)
Location Y	Location on the vertical axis of the fixture (in pixels)
Dispersion X	Horizontal dispersion of the fastener (in pixels)
Dispersion Y	vertical dispersion of the fastener (in pixels)

**Table 8.** Raw data from the EVENT file in the case of a fixation

Start	Blink start time (in $\mu\text{s}$ )
End	Blink end time (in $\mu\text{s}$ )
Duration	Blink duration (in $\mu\text{s}$ )

**Table 9.** Raw data from the EVENT file in the case of a blink

These three types of ocular events are defined as follows:

- A fixation corresponds to a phase in which the position of the subject's gaze varies only slightly in space: there are only micro-movements in the eyes.
- A saccade corresponds to eye movement with a speed of at least  $30^\circ/\text{s}$
- A blink is a short downward movement of the eyelid lasting about 100 ms.

The nature of the ocular event (fixation, saccade or blink) is carried out by means of a Begaze algorithm which requires, in particular, as input data: the position of the gaze, the position of the head and the position of the eyes. Parallel to the output files " Sample " and " Event ", the Begaze software allows to extract the recorded video from the scene camera (Figure 24). It is therefore possible to visualize posteriori the visual exploration of the subject during the whole eyeglass phase.



**Figure 24.** An image recorded by the stage camera (first person view)

## VI. DATA PROCESSING AND ANALYSIS

The final objective of the classification system elaborated in this work was to be able to correctly differentiate a healthy subject from a subject suffering from frontotemporal dementia and therefore from apathy.

The types of data collected during the ECOCAPTURE protocol for each subject were first analyzed and processed individually. Afterwards, they were compared and assembled as the only input of the final classification and regression system, in order to achieve the goal of finding a behavioral signature of apathy for bvFTD patients. To process the data and to elaborate the classification system, Matlab, R environments were used for statistical analysis and SPM12 software was very useful for the analysis of functional MRI images.

The data processed in this thesis are derived from a dataset of 27 subjects, including 12 healthy volunteers and 15 bvFTD patients (Table 10).

	<b>1 (MALE)</b>	<b>2 (FEMALE)</b>	<b>Total</b>
<b>FTD</b>	<b>9</b>	<b>6</b>	<b>15</b>
<b>HC</b>	<b>5</b>	<b>7</b>	<b>12</b>
<b>Total</b>			<b>27</b>

*Table 10. Dataset of subject, for type (FTD and HC) and sex (MALE and FEMALE)*

### 6.1. DEMOGRAPHIC CHARACTERISTICS OF THE SUBJECTS

The demographic characteristics and the MMSE (mini mental state) score are described in Table 11, together with the result of the ANOVA test, applied for these variables in order to identify particular similarities or differences. No significant differences were found between the two groups by age, gender and educational level. BvFTD subjects had an overall MMSE score lower compared to HC; applying the ANOVA test, a significant difference ( $p < 0.001$ ) was found between the 2 groups.

	HC (n=12)	FTD (n=14)	ANOVA	Comparison
Gender (M/W)	5/7	8/6	n.s.	
Age	46-71 (63.6)	45-82 (63.7)	n.s.	
LE	4-8 (7.3)	2-8 (6)	n.s.	
MMSE	28-30 (29.33)	20-29 (23.07)	F = 66.388 p = 2.279e-08 ***	FTD < HC (p < 0.001)

**Table 11.** General characteristics of the population, M = male; F= female; LE= level of education; ns= non-significant

## 6.2. BEHAVIORAL MATRICES

The previous sections described how *The Observer XT*®:

1. Allows observation and recording of the subject's behavior (Figure 25) using an ethogram;
2. Provides the video-based behavioral metrics as records attached to a timestamp; and exports the course of events (behavior) into an annotated csv file (Table 12).

Time Relative_hms	Time Relative_sf	Duration sf	Subject	Behavior	Modifier Exploration	Modifier Activity	Event Type
00:00:12	12	3	FTD 2	Exploration	Draw Unit		State start
00:00:15	15	0	FTD 2	Walking			State stop
00:00:15	15	10	FTD 2	Standing			State start
00:00:15	15	0	FTD 2	Exploration	Draw Unit		State stop
00:00:15	15	7	FTD 2	Exploration	Books / Magazines		State start
00:00:22	22	0	FTD 2	Exploration	Books / Magazines		State stop
00:00:22	22	6	FTD 2	Activity		Reading	State start
00:00:25	25	0	FTD 2	Standing			State stop
00:00:25	25	4	FTD 2	Walking			State start
00:00:28	28	0	FTD 2	Activity		Reading	State stop
00:00:29	29	0	FTD 2	Walking			State stop
00:00:29	29	7	FTD 2	Standing			State start

**Table 12.** Video-based behavioral attached to timestamp

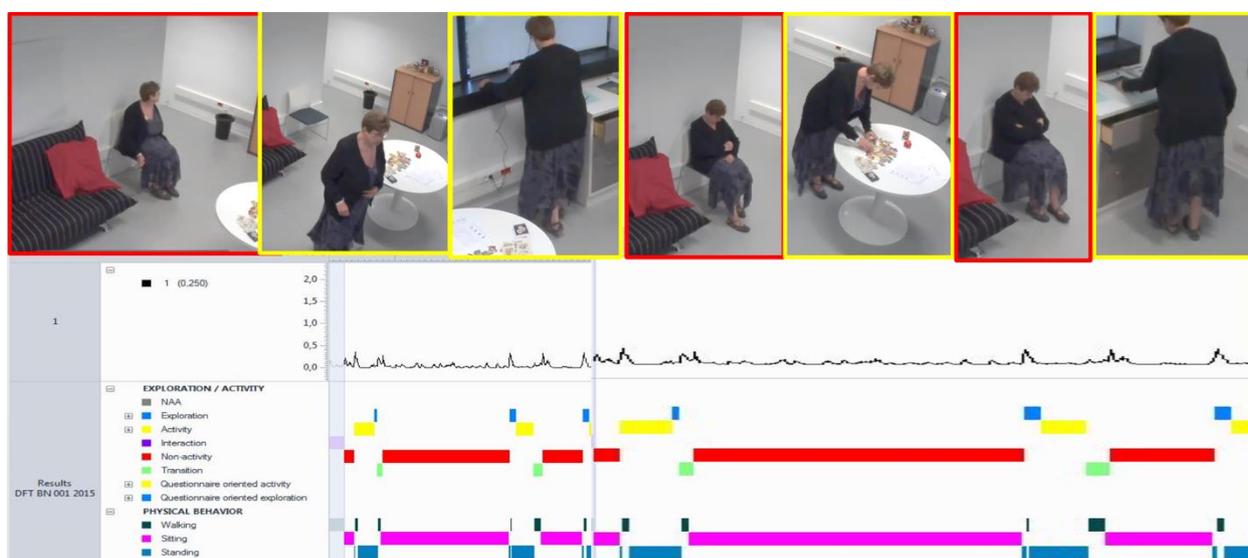
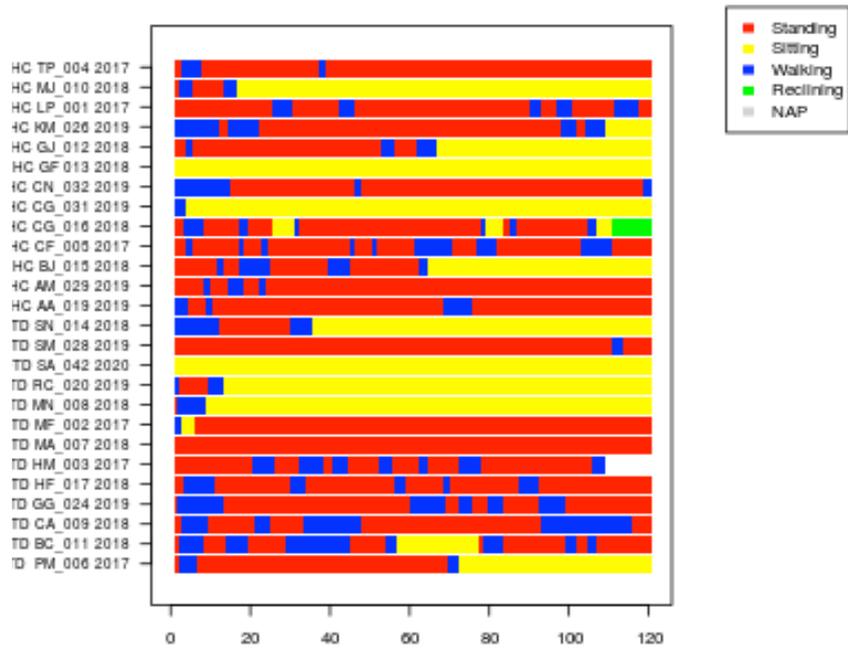


Figure 25. Observation and recording of the patient's behavior

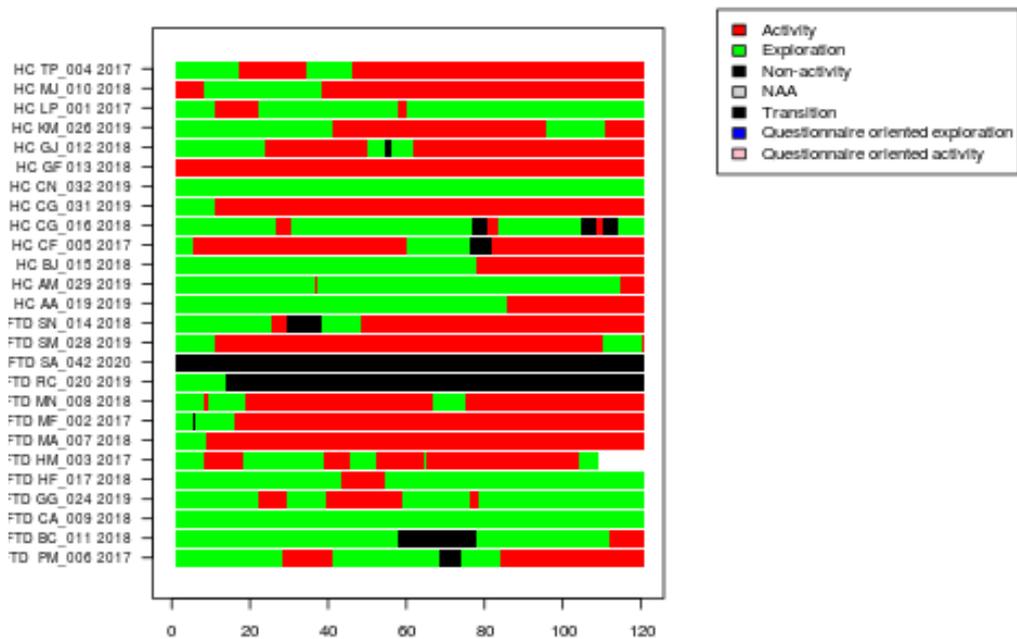
It's been analyzed the set of exported csv files to create behavioral matrices. These matrices were composed in the form of dummy-code (1= PRESENCE of a specific behavior, 0= ABSENCE of a specific behavior) and computed by a Matlab script. The various activities performed by the subjects, as well as their physical position, both during the free phase and the guided phase, were recorded for every second. The behavior is coded on the basis of the ethogram and recorded into two behavioral matrices, each at a frequency of 1 Hz (one state per second). The final output of this algorithm is time-series behavioral matrices, with one row per subject.

For the whole duration of the free phase (FP, 420 s) and the guided phase (GP, 600s), we identify at any time (every second), the subject's state according to two state diagrams. For example, a subject who is sitting and without activity is in the "sitting" state and in the "non-activity" state. Therefore, the columns in the first matrix (Figure 26) correspond to the activity, while the columns the second matrix (Figure 27) correspond to the physical position.

Finally, the time-series behavioral matrices of dummy-codes, present in a differentiated way, behavior for the HC (top sub-matrix) and for bvFTD patients (bottom sub-matrix), for both the free phase and guided phase.



**Figure 27.** Physical Posture Times-Series matrix with one row per subject (rows 1-13: HC; rows 14-26: bvFTD) with columns corresponding to the physical posture during 120 seconds (1 Hz) for each subject. In regard to the class called “posture”, we defined four categories: Reclining (green), Sitting (yellow), Standing (red) and Walking (blue).



**Figure 26.** Activity Times-Series matrix with one row per subject (rows 1-13: HC; row 14-26: bvFTD) with columns corresponding to the activity/exploration during 120 seconds (1 Hz) for each subject. In regard to the class called “activity”, we defined three categories: Activity (red), Exploration (green) and Non-Activity (black).

These processed data and visual representations will be relevant and leading the way to develop new methods (e.g. pattern recognition) for differentiating healthy subjects from patients with a specific level of apathy. Another step would be the creation of the dummy-code behavioral matrices from a more detailed level, due to the various sub-behaviors that are part of the categories included in the "ACTIVITY" section, in the "EXPLORATION" section, "Questionnaire oriented activity", "Questionnaire oriented exploration". This further differentiation of the sub-activities will therefore be an additional label to characterize apathetic patients and healthy volunteers.

By summing the matrices by group (Figure 28, Figure 29), we obtained a behavioral signal per state of activity (i.e. activity, exploration, non-activity) for each type of subject (HC vs bvFTD). This representation and this format of information "are very promising" for the further development of classification methods. Indeed, the activity signal (red) and the exploration signal (green) appeared to be different between the HC group and the bvFTD group. For the HC (Figure 29), the green curve (exploration level) is above the red curve (activity), then the curves intersect and the exploration level is below the activity level. For the bvFTD (Figure 28), the curves (activity and exploration) are quite similar, from some times. These figures show that HC and patients presented a specific behavioral pattern, particularly during the very first minutes they entered and discovered the room. This result confirms through another method, the result reported by Batrancourt et al. [2]. Facing with a new environment, HC first explored it for a short period of time and then engaged in sustained activity. In contrast, bvFTD patients were characterized by greater inactivity and less exploration/activity than HC. This exploration deficit under ecological is a behavioral indicator of apathy in frontotemporal dementia.

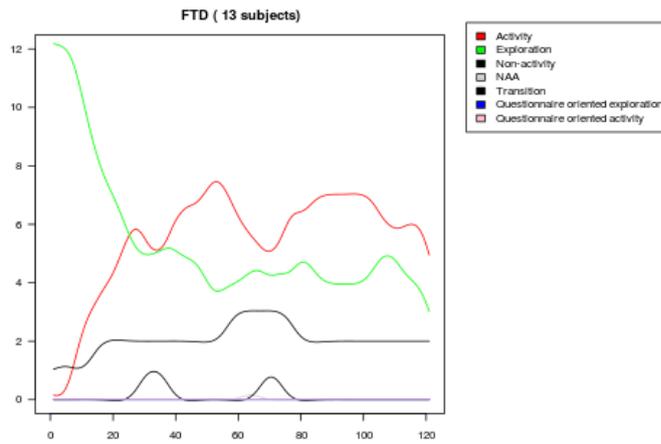


Figure 28. Signal integration from 13 bvFTD matrices.

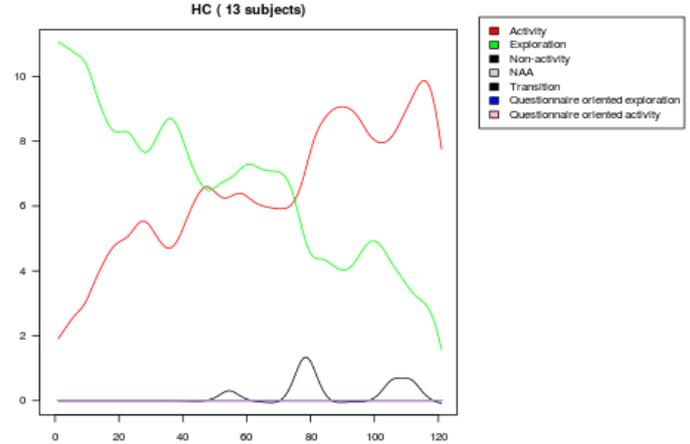


Figure 29. Signal integration from 13 HC matrices.

### 6.3. NEUROPSYCHOLOGICAL DATA

Subsequently, from the rather abundant set of neuropsychological data, the most significant ones were selected, in order to use them as input for a clustering algorithm aimed at correctly differentiating HC from bvFTD. The neuropsychological balance sheet is the result of a series of tests and questionnaires, imposed on each subject in this study, which aims to provide a clinical evaluation of apathy.

MMSE	Mini-mental state
SAS	STARKSTEIN Apathy Scale
FAB	Rapid Frontal Existence Battery: Assessing Dysexecutive Syndrome
MATTIS	MATTIS Dementia Rating Scale (DRS).
MINI-SEA	Mini-Social Cognition & Emotional Assessment.
HAD	Hospital Anxiety and Depression scale
HAD ANXIETY	HAD ANXIETY
HAD DEP	HAD DEPRESSION
HAYLING	Cognitive disinhibition HAYL_A HAYL_B HAYL_BA HAYL_ERR

Table 13. List of selected variables for clustering technique application

For some subjects there was a lack of some data, due to the lack of response in some questionnaire requests. In these cases the missing data was replaced by the median of the

values for that category of HC if he/she was a healthy volunteer or bvFTD if he/she was a patient. This technique known as "median imputation" therefore ensures that the analysis is not improperly interrupted.

### *6.3.1. Principal components analysis (PCA) clustering*

It's been applied the technique of analysis in principal components (PCA) to the set of descriptive variables (scores) from the neuropsychological assessment. The PCA is a set of statistical techniques whose aim is to significantly reduce a more or less vast group of variables describing a phenomenon. The result of this analysis is the creation of a number of "latent" variables, less than the initial quantity of variables, which can equally describe the statistical phenomenon without losing information [23]. A new cartesian plane is then created on the axes of which the variables are projected, in descending order with respect to the value of their variance.

Considering only the main ones among these, a reduction in the complexity of the number of variables is made.

From the PCA chart of variables it is possible to distinguish:

1. First cognitive performance dimension (MMSE, MATTIS, FAB);
2. Second dimension associated with the clinical evaluation index of apathy (SAS) and the depression index (HAD\_DEP);
3. Third dimension associated with cognitive disinhibition (HAYL\_A, HAYL\_B, HAYL\_BA).

The whole is clearly visible and is reflected in the correlation table of the variables ranging from -1, (red = negative correlation) to 1 (blue = positive correlation), in which the three poles identified by the three new main dimensions can be clearly seen (Figure 30).

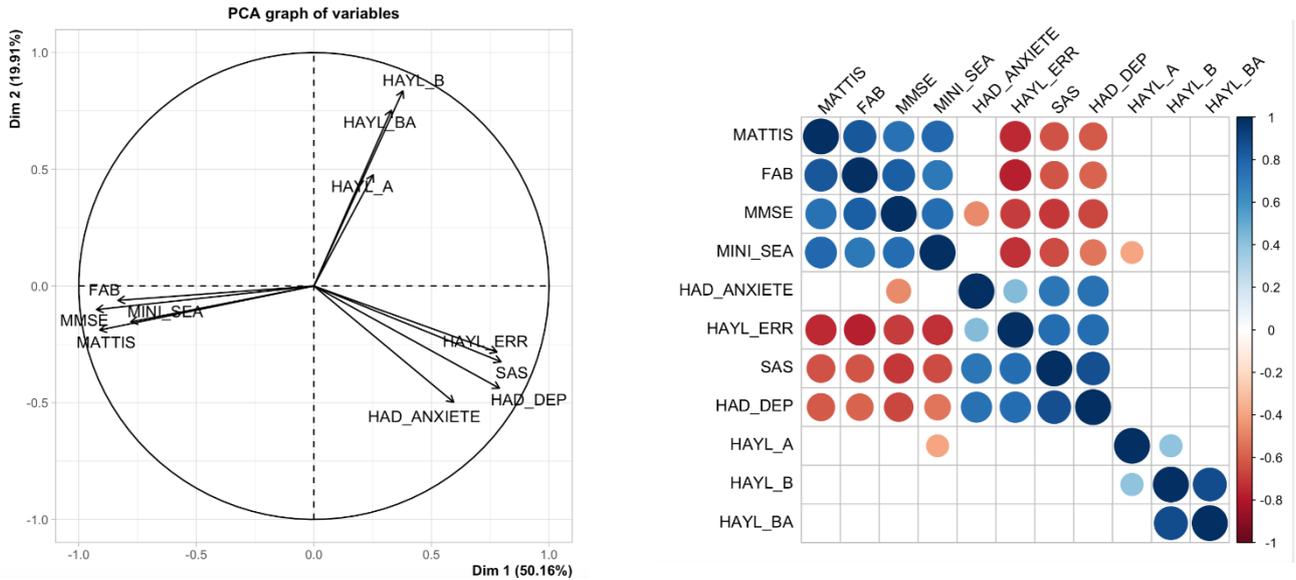


Figure 29. ACP Cartesian diagram and table of correlations between variables

By projecting the dataset of subjects in the new Cartesian plan composed by the two main dimensions, two clouds of subjects, the HC and the FTD clouds, are visualized, very distinct and separated one from the other (Figure 30). We saw that the dispersion is very extended in the bvFTD cloud, suggesting there are several sub-groups and profiles of bvFTD patients.

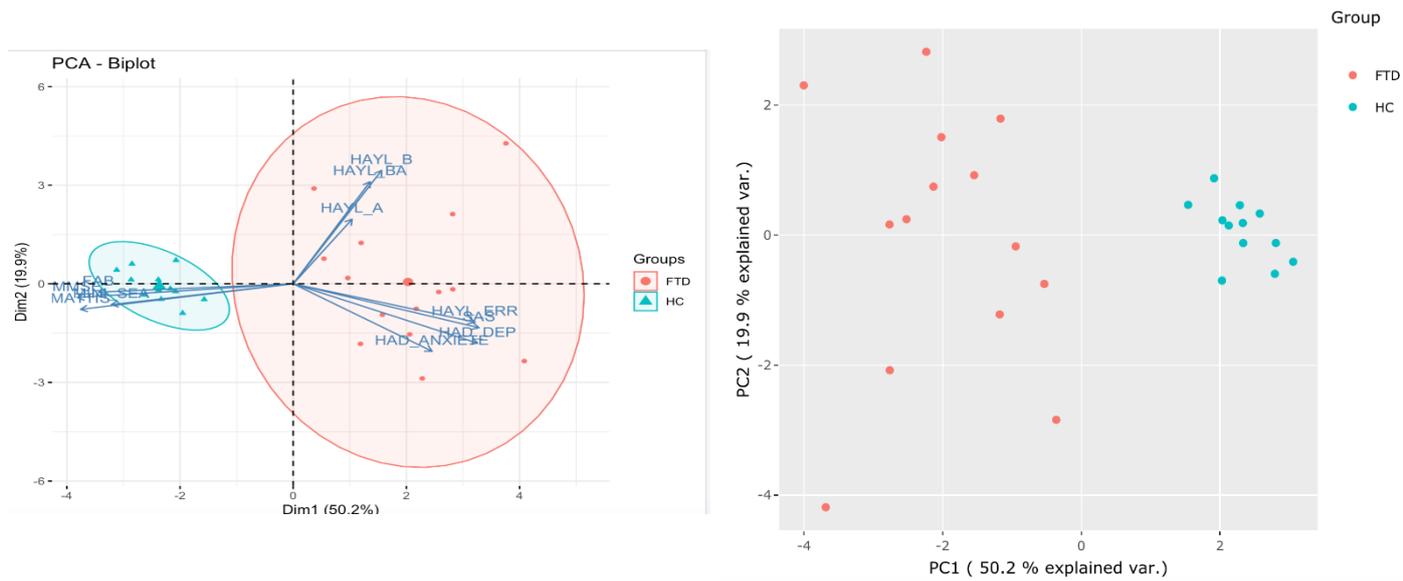


Figure 30. Division of subjects in two different clusters (bvFTD and HC) through ACP clustering technique

After an initial study of the variables and an initial distinction between healthy volunteers and bvFTD patients, several clustering techniques were applied, with the aim of differentiating, with regard to the category of apathetic patients, those with a higher overall level of apathy. The result was to find two different categories of apathetic patients, based on the neuropsychological assessment. The clustering technique was selected to provide a more precise distinction between the two categories. The clustering techniques were applied and tested using Matlab algorithms.

### 6.3.2. Relationship between apathy and cognitive disinhibition

A further representation of the subjects is the Cartesian plane, with the values SAS on the x axis and those of HAYLA-HAYLB on the y axis (Figure 31). In this way all subjects were represented according to their clinical level of apathy, depending on the level of cognitive disinhibition.

The choice of this additional graph is linked to the fact that cognitive disinhibition is closely related to apathy. FTD patients with a certain level of apathy usually also tend to have a rather high degree of cognitive disinhibition. It is precisely to cognitive disinhibition that certain behavioral characteristics of apathy are linked, such as the appearance of inappropriate behavior, strong impulsiveness and sociopathy.

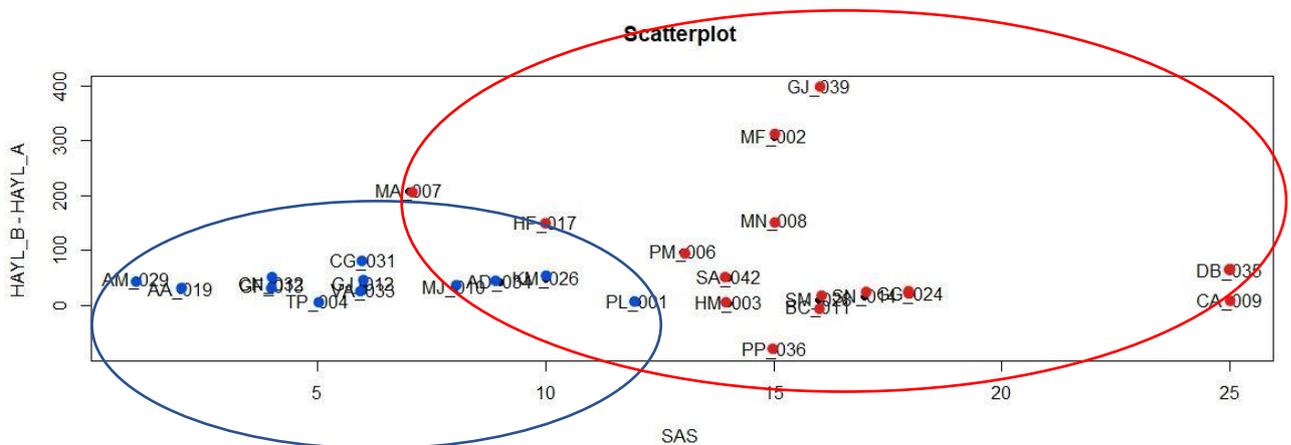


Figure 31. Scatterplot of subjects considering HAYLING and SAS variables

As can be seen from the Cartesian diagram above, FTD patients are visibly separated from healthy volunteers. It can be seen that, apart from some borderline cases, FTD patients not only have a rather high level of apathy (SAS), but also a higher level of cognitive disinhibition than healthy volunteers overall.

From this graph we therefore obtain two particularly distinct areas of subjects.

### 6.3.3. Clustering with SOM (Self-organizing Neural Networks) technique

This clustering technique is based on unsupervised learning, therefore does not require initial labelling of the training set and is a type of neural network. During a training phase the neural network receives a number of input models and learns how to classify them, based on links between them [14].

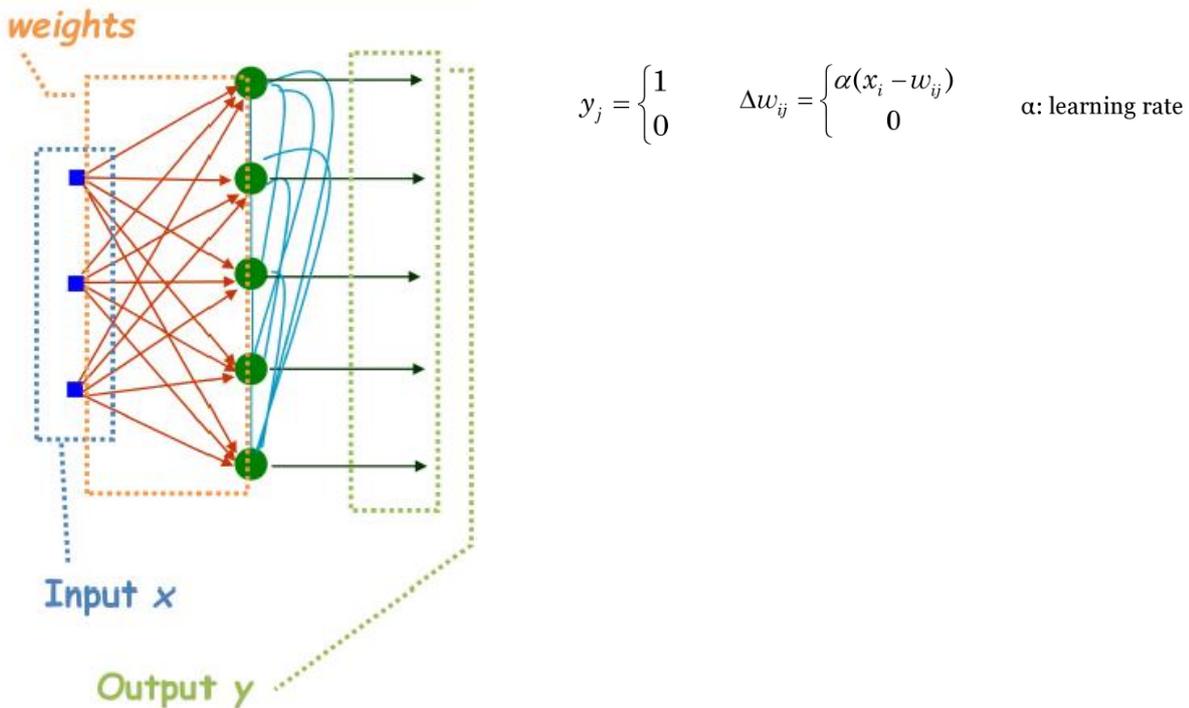
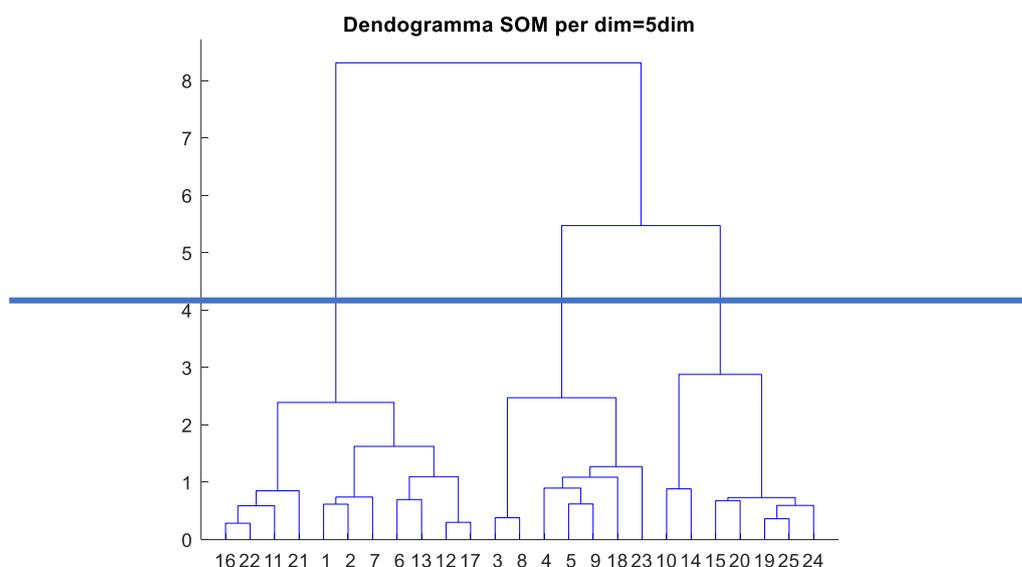


Figure 32. SOM network operation diagram.

The dendrogram (Figure 33) on which the operation of the SOM network is based has been divided in such a way as to obtain three clusters. In order to evaluate the efficiency and reliability of this technique, the inter-cluster distance and the intra-cluster variance have been calculated, which will be subsequently compared with those of the other unsupervised learning techniques. In particular, the intra-cluster variability is the sum of the distances between each element belonging to the cluster is the centroid of that particular cluster (Table 14); the inter-cluster distance represents the distance between two centroids. The Euclidean distance is used as the type of distance for the calculation of the `dist_inter` and `var_intra`. In addition, three classification errors occurred.



**Figure 33.** Dendrogram on which the SOM network is applied

VAR INTRA	5.225
DIST INTER	0.4717
CLASSIFICATION ERRORS	2

**Table 14.** Variance intra-cluster, distance inter-cluster and classification errors of SOM.

### 6.3.4. Clustering with K-means technique

The k-means is one of the most widespread unsupervised learning algorithms and divides the elements of a dataset into a predefined number of clusters in order to minimize intra-cluster variability and maximize inter-cluster distance. This will result in clusters of elements (clusters) that are homogeneous and distinct from each other.

For each cluster a centroid is defined, i.e. a precise reference point at the centre of each cluster representing the average value of all elements of each cluster [24]. The centroid is an element that, in the k-means, is continuously updated during the iterative process in order to optimize the subdivision of the elements of the dataset. This process occurs as long as this subdivision remains unchanged from one iteration to another. The number k of clusters is chosen arbitrarily at the beginning of the iterations.

The k-means has been applied to the subjects' dataset, considering the neuropsychological data, with the aim of subdividing them, as has been done for the SOM algorithm, into three categories. The first one was composed of healthy volunteers and two others based on two different levels of apathy progress.

In order to have a division into more homogeneous groups all the data of each subject have first of all undergone a normalization with respect to the maximum value so that in the new dataset there were only values between 0 and 1.

In this way the precision of the division into clusters is increased.

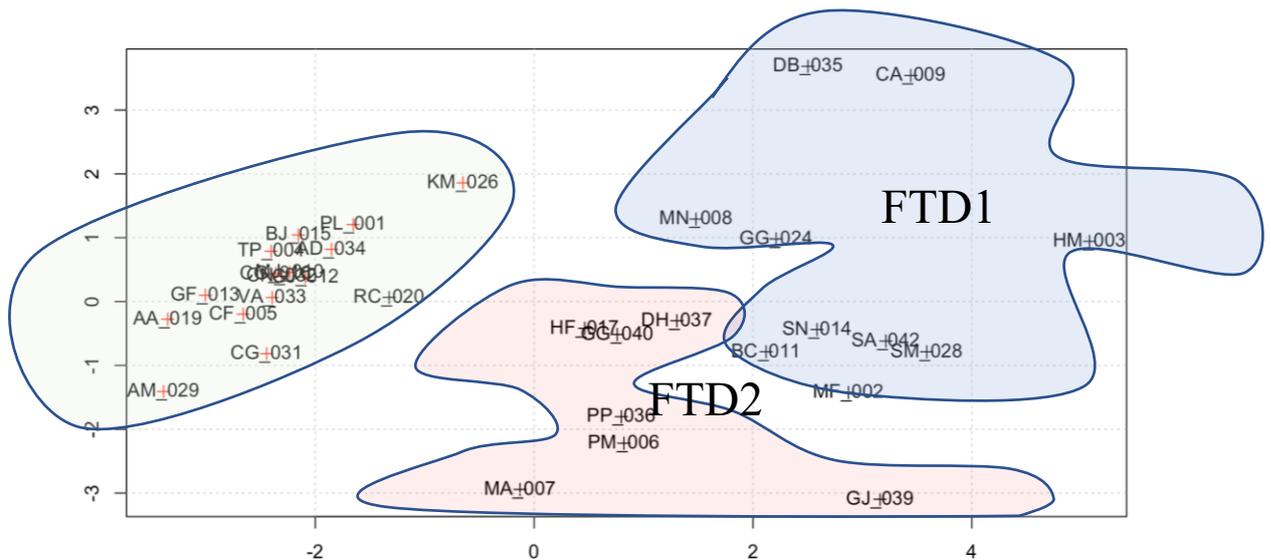


Figure 34. Clustering division by k-means technique

VAR INTRA	1.88
DIST INTER	6.18
CLASSIFICATION ERRORS	0

**Table 15.** Variance intra-cluster, distance inter-cluster and classification errors of *k*means

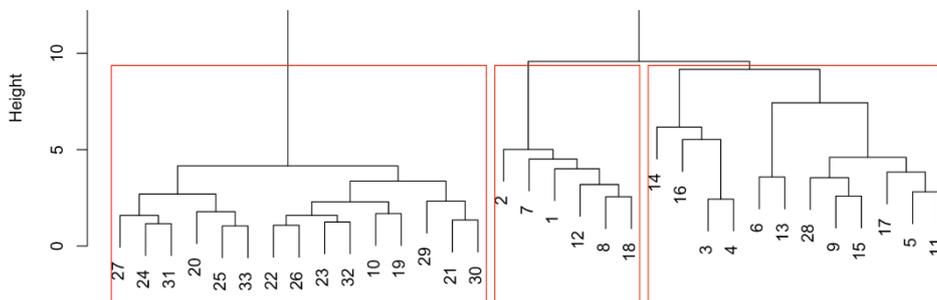
As can be seen from the results obtained (Table 15), the intra-cluster variability has a very low value, compared to the distance between clusters and there are no classification errors. In addition, two groups of patients are distinguished.

### 6.3.5. Ascending hierarchical segmentation

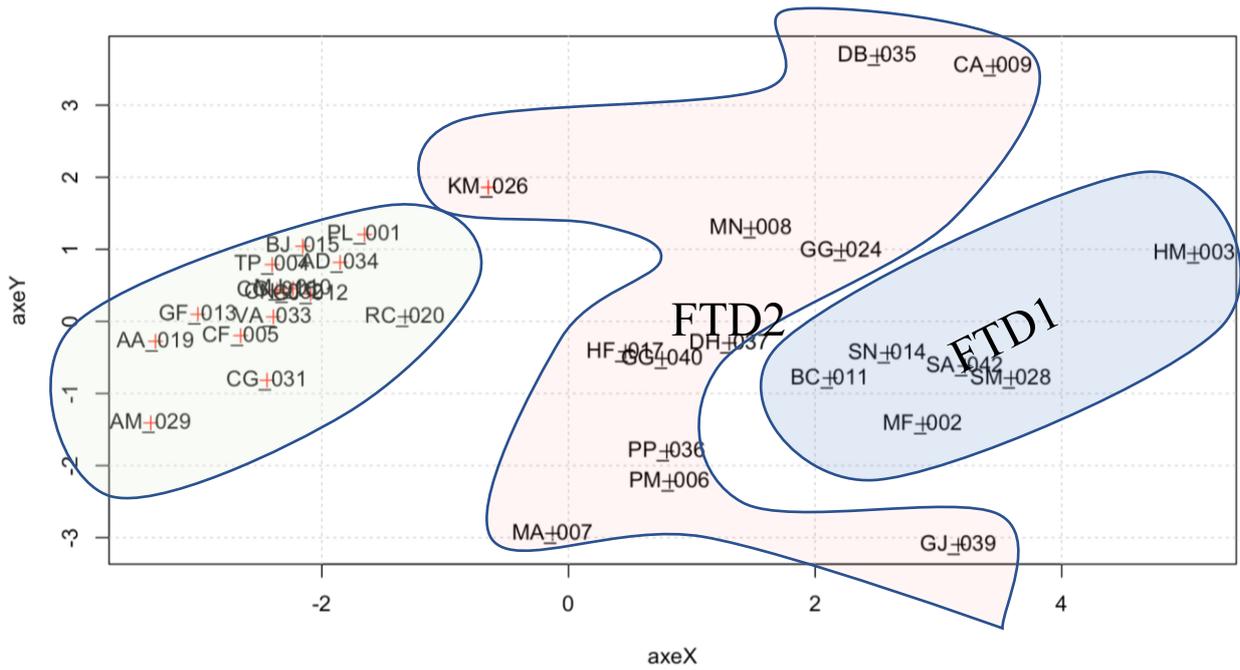
The third and last technique that has been tested for subdivision into clusters is hierarchical segmentation, ascending type.

The word ascendant explains how the objective of this technique is to define a group (cluster) starting from a set of individuals. To form clusters, this method uses the Euclidean distance as a measure of dissimilarity between individuals.

In our case the dendrogram (figure 36) is used to illustrate the hierarchy and clustering that is generated by the algorithm. Starting from the consideration of each subject as a cluster, based on the dissimilarity between individuals, the most similar clusters (figures 35) are grouped until they are as low and homogeneous as possible.



**Figure 35.** Dendrogram of ascending hierarchical segmentation



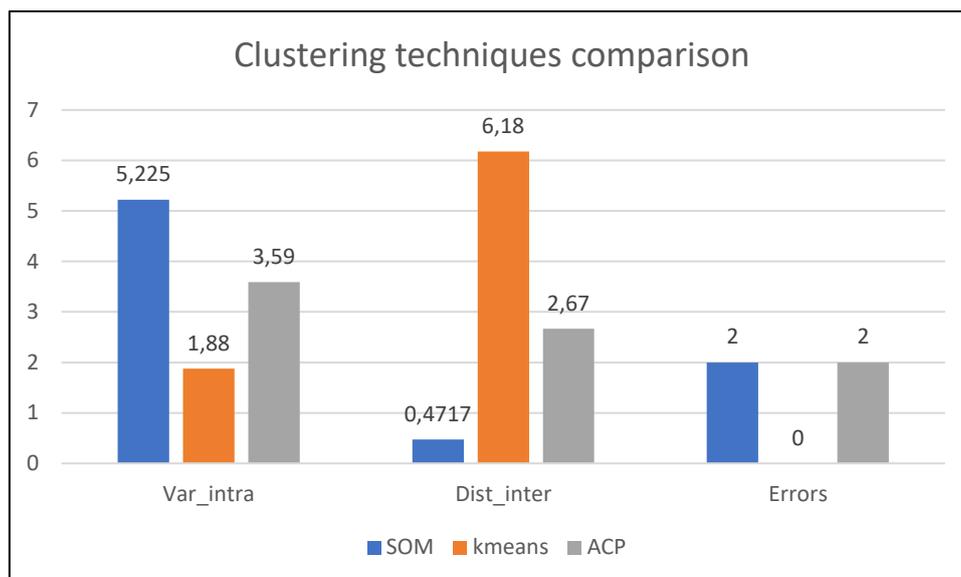
**Figure 36.** Clustering division by ascending hierarchical segmentation technique

Also in this case the inter-class distance and the intra-cluster variance were calculated, and then compared to the values of the two cluster techniques previously used.

VAR INTRA	3.59
DIST INTER	2.67
CLASSIFICATION ERRORS	2

**Table 16.** Variance intra-cluster, distance inter-cluster and classification errors of ascending hierarchical segmentation technique

After the application of these three clustering techniques through Matlab, the values considered valid to evaluate the one with the best level of precision were compared.



**Figure 37.** Comparison of variance intra\_cluster, distance inter-cluster and classifications error between SOM, kmeans and ACP clustering techniques

As can be seen from the graph, the k-means has the lowest value for the average intra-cluster distance and the highest value for the inter-cluster distance. Furthermore, it does not make classification errors, unlike the other two techniques.

For these reasons, the k-means is the most valid technique to obtain a more adequate subdivision of subjects into three clusters.

### 6.3.6. Comparison of neuropsychological variables between HC and FTD

In order to highlight the differences between the neuropsychological variables that allowed the division of the subjects into three clusters, the ANOVA test was applied to investigate significant differences between HC and bvFTD.

	HC (n=12)	BvFTD (n=14)	ANOVA	Comparison
<b>SAS</b>	1-12 (6.08)	7-25 (16.14)	F = 41.013 p = 1.272e-06 ***	BvFTD > HC (p < 0.001)
<b>FAB</b>	15_18 (17.25)	5-16 (11.43)	F = 29.915 ;	BvFTD < HC

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			p = 1.273e-05 ***	(p < 0.001)
<b>SEA-REC</b>	11.14-14.57 (12.57)	4.71-12 (8.39)	F = 36.194 p = 3.275e-06 ***	BvFTD < HC (p < 0.001)
<b>SEA-FP</b>	11.25-15 (13.4)	2.25-15 (8.52)	F = 18.66 p = 0.0002342 ***	BvFTD < HC (p < 0.001)
<b>MATTIS</b>	141-144 (142.5)	104-135 (118.8)	F = 77.107 p = 5.838e-09 ***	BvFTD < HC (p < 0.001)
<b>HAYL-BA</b>	6-80 (35.87)	90.82-398 (88.96)	n.s.	
<b>HAYL-ERR</b>	0-7 (2.25)	5-45 (22.28)	F = 22.628 p = 7.705e-05 ***	BvFTD > HC (p < 0.001)
<b>HAD-A</b>	1-10 (4.5)	1-17 (8.28)	F = 5.8819 p = 0.02319 *	BvFTD > HC (p < 0.05)
<b>HAD-D</b>	0-3 (1.25)	0-12 (6.36)	F = 25.051 p = 4.103e-05 ***	BvFTD > HC (p < 0.001)

**Table 17.** Application of ANOVA TEST for Neuropsychological variables

The ANOVA test showed a significant difference ( $p < 0.001$ ) for apathy (SAS) between the two groups. According to SAS, bvFTD patients are therefore more apathetic than VS. Apart from one of two scores measuring disinhibition (HAYL\_BA), the ANOVA test showed significant differences between the two groups, for all neuropsychological scores (Table 17). With regard to cognitive function, bvFTD patients presented lower scores than healthy volunteers; on the other hand, bvFTD patients have higher scores of anxiety and depression than healthy volunteers. Concerning disinhibition, bvFTD patients have higher scores than HC. finally, with regard to social cognition, bvFTD patients had lower scores than HC subjects.

#### 6.4. ACCELEROMETER DATA

Among the data obtained thanks to the use of the "Movisens" sensor, the intensity and sign of the three acceleration components (Ax, Ay, Az) were particularly significant in order to differentiate bvFTD patients and HC. In fact, after having extracted the three components from the sensor,

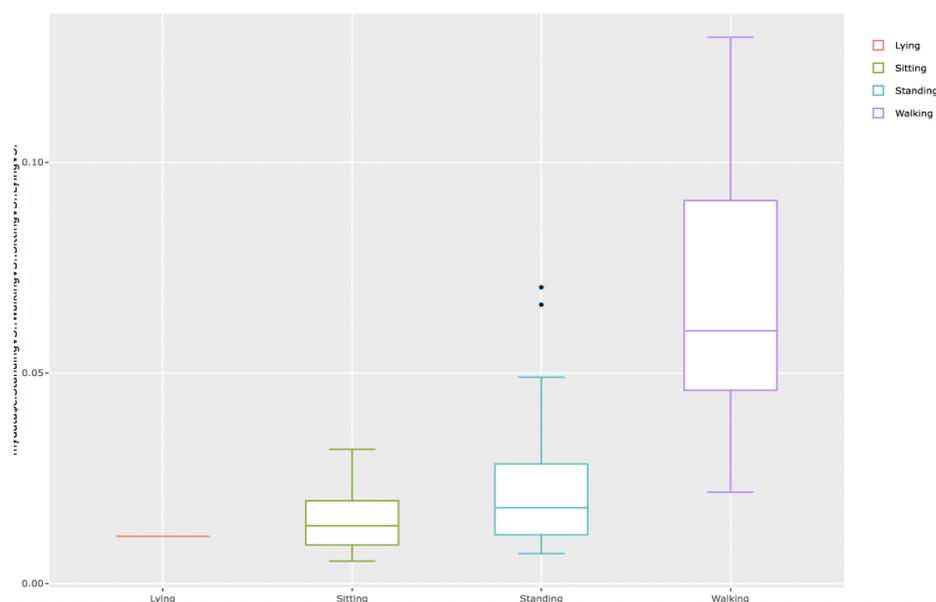
using a Matlab algorithm, the average acceleration during the recording time of the free and guided phase was calculated, in order to then make comparisons.

$$Acc_T = |\sqrt{Acc_x^2 + Acc_y^2 + Acc_z^2} - g|$$

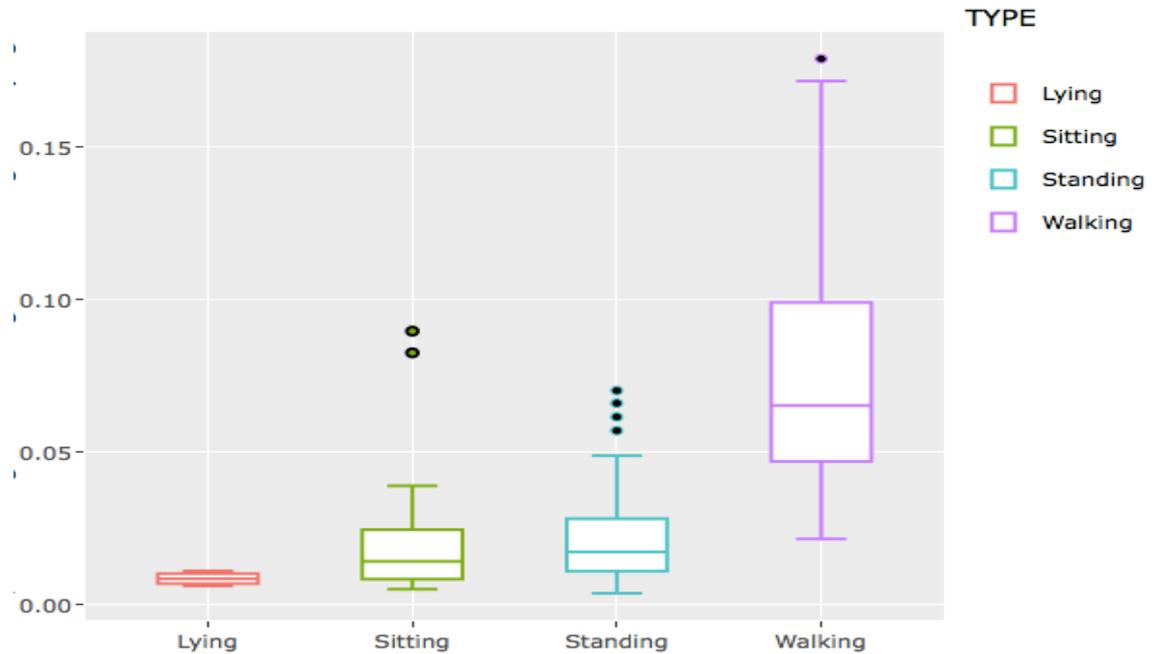
Subsequently the average acceleration was segmented in the recording time, using 64 Hz (accelerometer acquisition frequency) as the sampling frequency, so that the average acceleration can be obtained during specific activities.

### 6.4.1. Differentiation of the three types of behavioral occurrences

The first analysis performed was to verify that, considering both the free and the guided phase, the sensor provided a real difference in the intensity of the acceleration between a walking, sitting, standing state, both for healthy volunteers and FTD patients. In order to do this, boxplots were plotted using the R software to graphically display the differences:



**Figure 38.** Boxplot of mean acceleration as a function of the type of behavioral occurrence for HC volunteers



**Figure 39.** Boxplot of mean acceleration as a function of the type of behavioral occurrence for bvFTD patients

As can be seen from the different boxplots, the one representing the walking state has an average, a first and third quartile that is considerably higher than the other states.

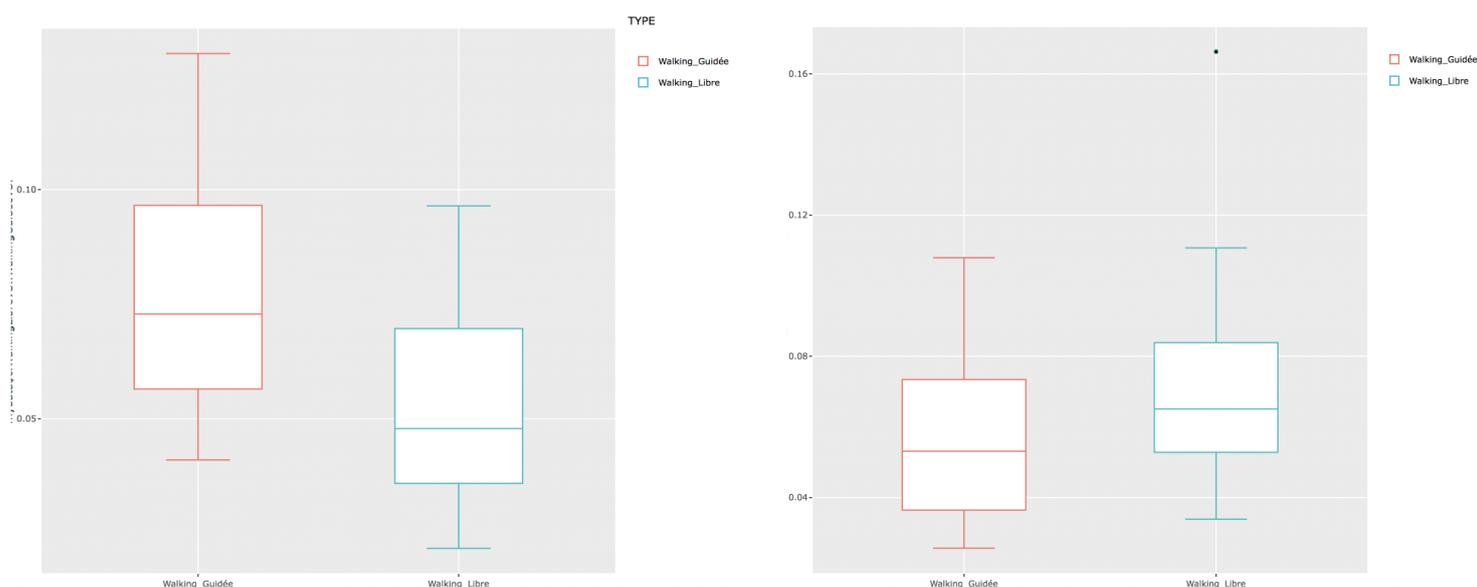
In order to have further statistical evidence, the Wilcoxon-test was applied, which demonstrated the difference in values between the states ( $p\text{-value} < 0.05$ ).

P-value (HC)	Standing	Walking		P-value (FTD)	Standing	Walking
Sitting	0.6924	3.147e-8		Sitting	0.17369	5.371e-16
Standing		2.2e-16		Standing		5.801e-14

**Table 18.** Wilcoxon test for mean acceleration as a function of the type of behavioral occurrence (left HC and right patient bvFTD)

### 6.4.2. Differentiation of a type of behavioral occurrence according to phase (free, guided)

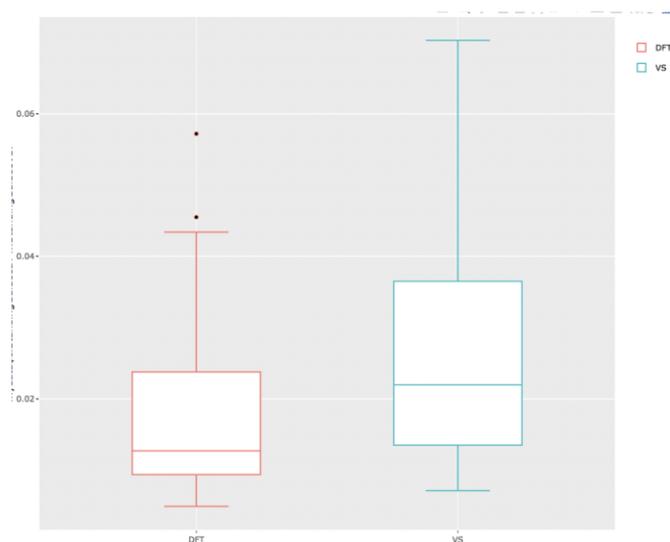
The second analysis carried out is based on the value of the average accelerations of the activities represented in the previous paragraph according to the type of phase, free or guided. As far as the trend of the average accelerations during the sitting and standing phase is concerned, no significant differences emerged, both for healthy volunteers and FTD patients.



**Figure 40.** Boxplot of mean acceleration as a function of the type of behavioral occurrence (left HC and right patient bvFTD)

However, the average acceleration of the walking occurrences in the guided phase was greater than the walking occurrences in the free phase in healthy volunteers ( $p$ -value = 0.011). In addition, for FTD patients the average acceleration does not vary significantly between the free and guided phase.

Concerning standing position as well, the average acceleration of healthy volunteers was significantly higher than that of FTD patients in the guided phase ( $p$ -value = 0,03543).



**Figure 41.** Boxplot of the average acceleration in standing during the guided phase

The differences in the average acceleration of gait per phase of the scenario in FTD patients and healthy volunteers can be explained by several reasons.

Firstly, it seems that during the free phase, healthy volunteers have more difficulty than FTD patients in ignoring the cameras. Initially, healthy volunteers tend to feel observed, while FTD patients, probably due to their social disabling or memory disorder, find it easier to manage the cameras or even pay no attention at all.

The guided phase took place 14 minutes after the start of the experiment, giving healthy volunteers time to get used to the presence of the cameras. Moreover, during this phase the behaviors are heterogeneous and no longer self-generating. Healthy volunteers find it easier to move around the room because most of the behaviors they will have will be "imposed" on them, so they will instinctively perform them.

#### 6.4.3. Mean acceleration during Eye-Tracking phase

Another type of analysis that was performed with regard to the accelerometer data concerned the trend of the average acceleration during the Eye Tracking phase. This was done in such a way as to be able to compare the average acceleration in some activities with the visual and ocular data provided by Eye Tracking glasses and have a more in-depth analysis.

To do this, it was necessary to implement a temporal segmentation of the various phases of the ECOCAPTURE protocol in order to obtain the average acceleration essentially during the Eye-Tracking recording period, from the precise moment the subject enters the PRISME room. This time period occurs as soon as after the end of the free phase and has a duration of about 7 minutes, like the free phase.

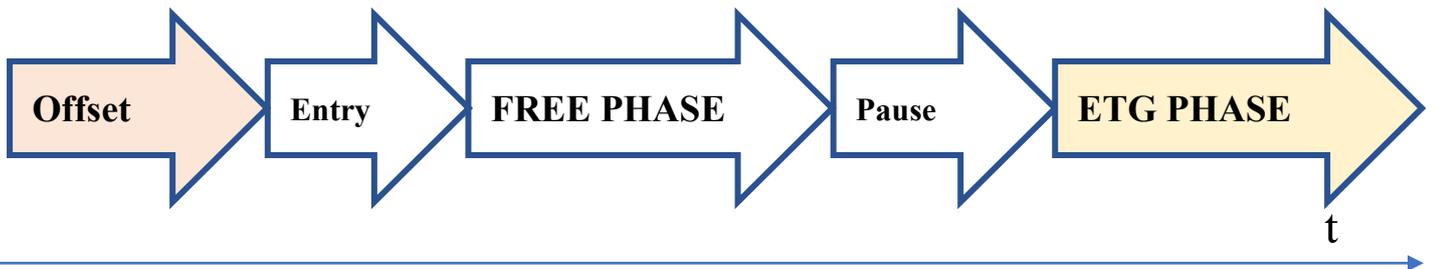


Figure 42. Temporal segmentation of different phases of ECOCAPTURE protocol

As can be seen from the Figure 42, for each subject there is an offset time in which there is a calibration and test phase, which is not indicated by the software *The Observer XT®* in the behavior recording. It is therefore necessary to subtract it from the total signal capture time of the accelerometer.

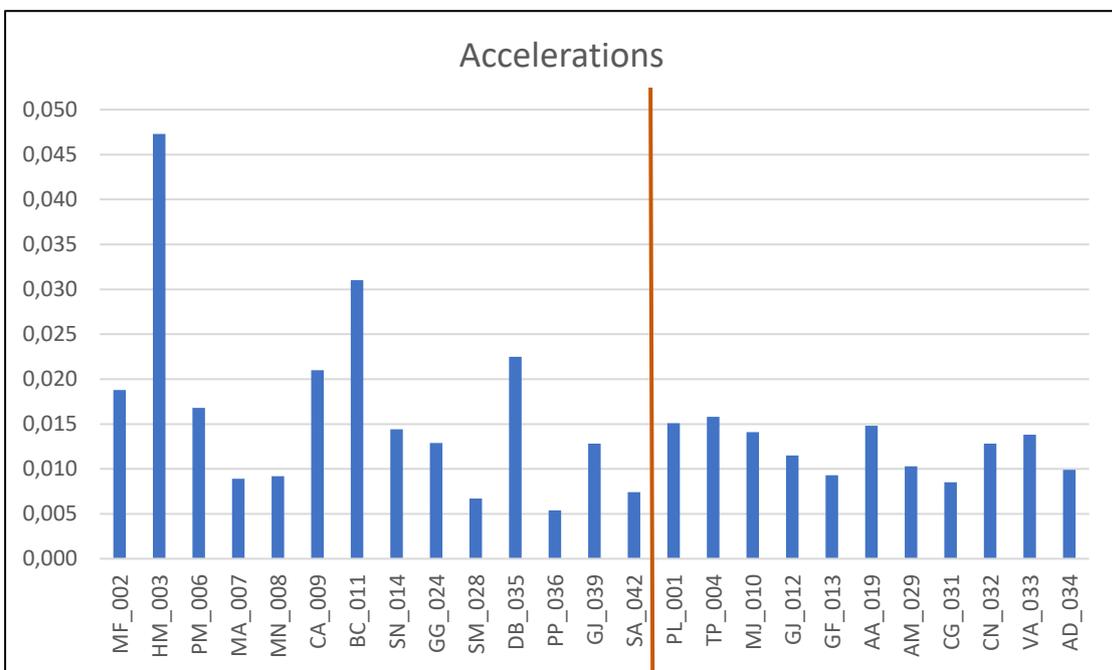


Figure 43. Trend of average accelerations during the ETG phase of the subjects, bvFTD patients on the left and HC on the right of the line.

From the graph (Figure 43) representing the trend of acceleration average in the ETG phase, we observe how bvFTD patients present a rather irregular trend of acceleration average, compared to HC that present a more regular and more uniform acceleration average.

## 6.5. EYE-TRACKING DATA

The Eye-Tracking technique is increasingly used in the clinical study of cognitive functions such as motor control, memory and motivation. In fact, eye movements can be seen as a reflection of the implementation of an action plan (locating an object), its realization (keeping one's gaze on the object) and its control (looking at the object again). However, each of these phases can be interrupted in an apathetic subject. In previous studies, it has been established that the parameters of jumps in particular (speed, amplitude), vary considerably depending on whether or not there is a reward at the end of the action performed by the subject. Various parameters of the ocular behavior are correlated to the degree of motivation and apathy of the subject, such as the maximum speed of saccade. However, the attenuation mechanisms used by each individual during a specific and unique task are very different from those used in real life. For this reason, eye-tracking glasses (ETG) have been used under ecological conditions, which allow the observation of the subject's ocular behavior.

Typically, Eye-Tracking technology is used either with a fixed head in front of a computer screen where the subject performs various tests, or with glasses during various activities such as reading a newspaper or watching a film. In this case, these glasses have been used to obtain more details on the visual exploration of the subject during his or her evolution in the PRISME room, as well as on the eye events the subject will present during the seven minutes of recording [3].

The neuropathology of frontotemporal behavioral dementia mainly affects the frontal lobes. Located in the frontal lobe, the Frontal Eye Field (FEF) is a key area that contributes to the initiation and executive control of voluntary eye movements. The following hypotheses have been made:

- I. The initiation of voluntary eye movements will be reduced in subjects with bvFTD, e.g. with a lower frequency of saccades, leading to a decrease in the ability to visually explore a new environment.
- II. Thanks to the conservation of the FEF and the improved saccade capacity in healthy subjects, the spatial distribution of the gaze will be more homogeneous in these subjects. Thus, a common pattern could be identified in HC, while in bvFTD subjects, the spatial distribution of gaze could have specificities for each participant.

The raw data collected from ETG glasses will be analyzed to show a difference in ocular behavior between HC and bvFTD patients.

A first task was to well understand what exactly each type of data in the EVENT and SAMPLE files corresponded to and to determine what was relevant to our analysis.

After an initial analysis, it was decided not to consider the pupil diameter data.

In an ecological context, in fact, these data cannot be interpreted as subject to factors external to the subject's degree of motivation, in particular variations in ambient light. The entire ETG data processing pipeline was performed using a MATLAB script.

The processing pipeline was applied only to the EVENT file and generated the variables needed for statistical analysis.

### *6.5.1. Pretreatment and quality-check*

The data has been cleaned up in order to exempt them as much as possible from any noise (data that is not useful or reliable). To do this, we removed the sequences at the beginning and end of the recording, corresponding respectively to the preparation time and the removal of the material. The objective of this step is to reduce the EVENT observation time to the time limits of the actual presence of the subject in the room. In addition, all Saccade events for which the maximum speed was higher than 800 degrees/sec have been eliminated, since a Saccade seems not to be able to exceed a speed of 800 degrees/sec, which is the established standard; in case of a maximum speed higher than 800 degrees/sec, it could be a misinterpretation of the event by the BeGaze software.

### *6.5.2. Calculation and description of ETG metrics*

All matrices and metrics presented were created from the EVENT file corrected by pre-processing. Several matrices have been created to generate the metrics (Table 19) and the temporal and/or spatial distribution figures of the events:

- OBS100Hz: Creation of a time matrix of the duration of the observation in hundredths of a second that allows to integrate the signal from 1000,000 Hz to 100 Hz. The OBS100Hz matrix contains all the events, with one colour for each type of event. This matrix represents the time distribution of events during recording.

- OBS1Hz: Integration of the OBS100Hz time matrix into a 1Hz signal frequency matrix. The matrix includes 3 rows (one row per event type) and per column, the number of events per second.

Number of saccades	nb_sac
Number of fixations	nb_fix"
Number of blinks	nb_blk
Number total of events	ttev=nb_blk+nb_fix+nb_sac
Duration of observation in microsec	dEXPEms
Duration of observation in cent of sec	dEXPEcs
Duration of observation in dixième de sec	dEXPEds
Duration of observation in sec	dEXPEs
Total during of saccades	d_sac
Total during of fixations	d_fix
Total during of blinks	d_blk
Total during of combined events	ttdev = d_blk+d_fix+d_sac
Average number of jerks per second	NbSacSec
Average number of fixations per second	NbFixSec
Average number of blinks per second	NbBlkSec
Frequency of saccades	freqSacn = d_sac/ ttdev
Frequency of fixations	freqFixn = d_fix /ttdev
Frequency of blinks	freqBlkn= d_blk/ttdev
Mean Amplitude	Amplitude
Mean PeakSpeed	PeakSpeed
Mean Average Speed	Average Speed
Mean Peak Accel	PeakAccel

*Table 19. List of ETG metrics*

### 6.5.3. Graphical representation of temporal and spatial distributions

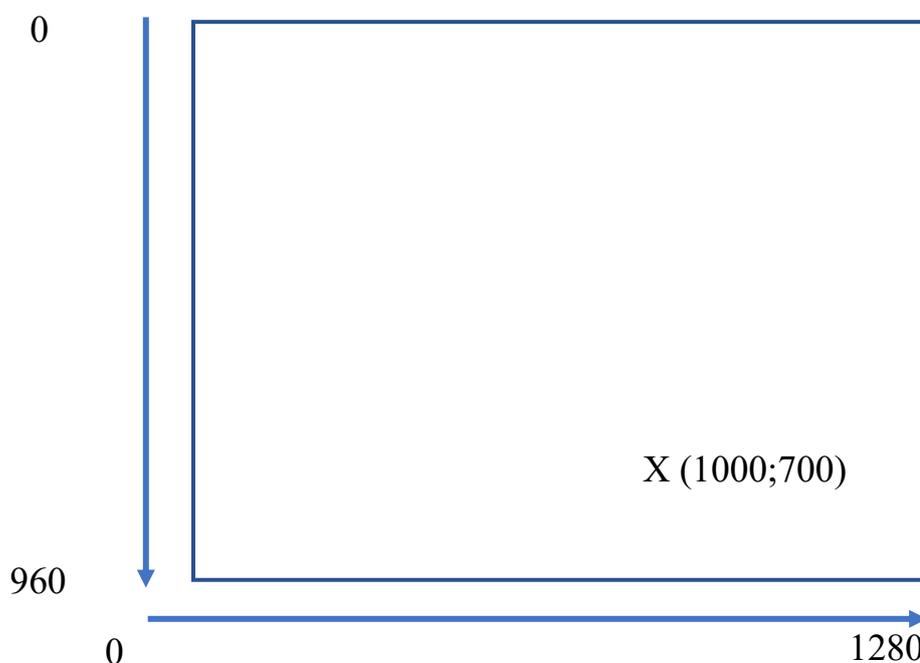
The visual representations of the subjects' data, as far as the temporal and spatial distribution is concerned, make it possible to take into account:

- I. The distribution of events over time;
- II. The visual path of the subject during data acquisition;
- III. The dispersion of the gaze through Heatmaps, i.e. graphic representations of data where the single values contained in a matrix are represented by colours. The objective is to identify particular and divergent visual models between groups of participants.

The Heatmap analysis of eye-tracking phase wanted to map was the position of the subject's eyes during that phase. The objective was to create a map of the areas explored by the subject using the data of the position of his or her eyes in binoculars.

Some activities that were repeated several times for all topics, such as reading a magazine, making coffee or making a puzzle, were selected as windows of interest. The analysis with HeatMap will be carried out during these windows of interest because they correspond to periods when the subjects have carried out similar activities. An analysis has also been carried out on a time window corresponding to the encounter of different types of activities.

In order to establish the HeatMap, we have imported into a first matrix on MATLAB the positions adjusted with the x and y binoculars (BPOR X and BPOR Y) for the duration of an interest window. These positions are expressed in pixels for an image of 1280 \* 960 pixels:



**Figure 44.** *Example of manhole position coordinates*

For example, in the image above the position of the gaze is marked with a cross, its coordinates in the frame are (1000; 700).

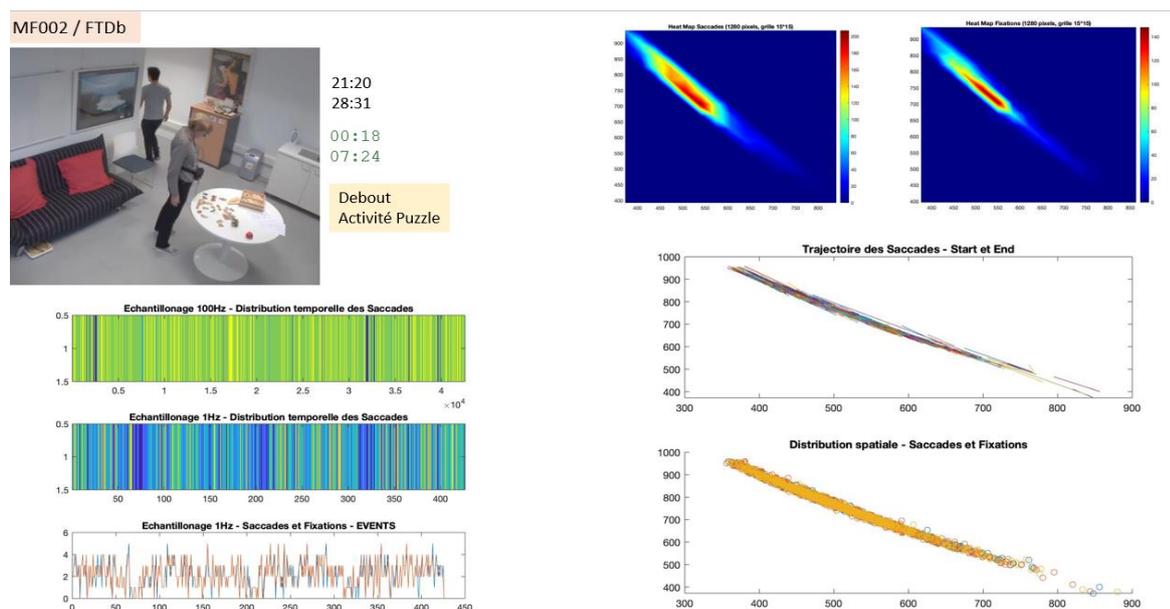
Then again thanks to MATLAB, the images recorded by the scene camera on this same window of interest were extracted one by one and then stored in a second matrix.

Then a MATLAB code was developed for the HeatMap itself: the higher the density of the points (a point represents the position of the eye in space at a given moment) on the same area of the image, the more this area was colored by a warm color (from the warmest to the coldest: red-

orange-yellow-green-blue). So the areas that were colored red were those in which the subject's gaze had been most often repeatedly during the duration of the window of interest. It is therefore possible to have an estimate of the degree of exploration and the degree of focus of the subject's gaze thanks to its HeatMap. Once all the images have been processed one by one, it is possible to make a video showing the evolution of the areas of focus of the subject's gaze on a window of interest.

Considering the same window of interest, the comparison of the HeatMap evaluation of two subjects allows, for example, to determine which of the two has the most homogeneous or extended spatial distribution of the gaze.

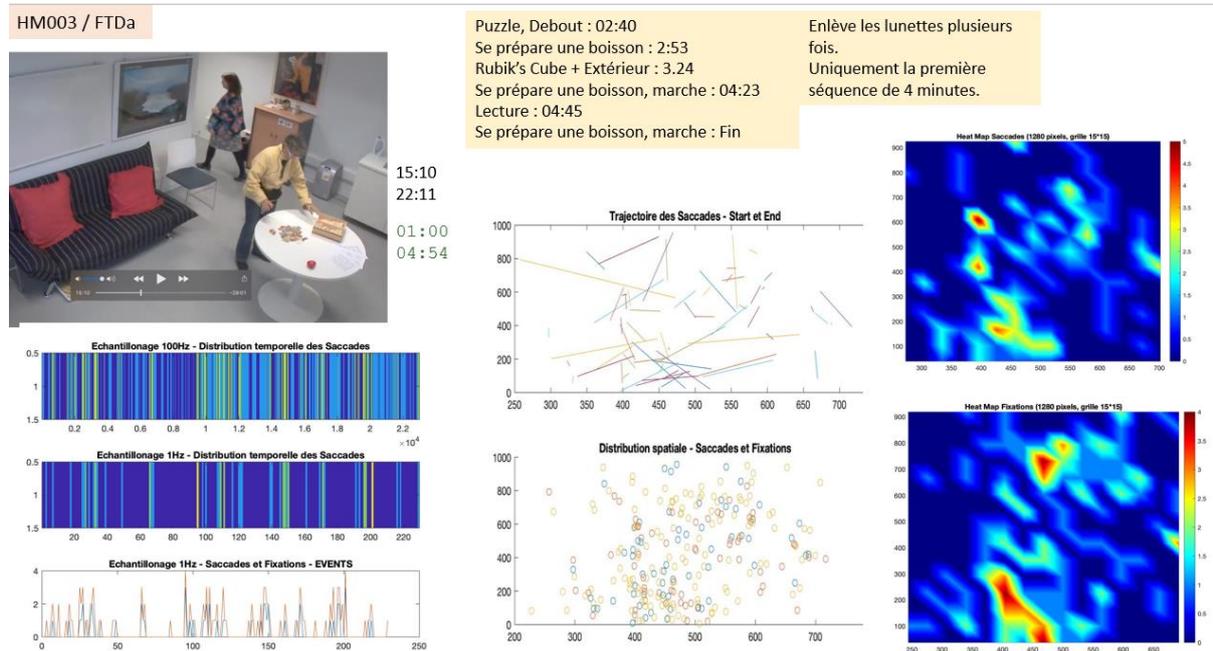
Subsequently, the aim is to identify particular and divergent visual patterns between groups of participants. The following figures highlight the ocular events and dispersion gaze for different subjects. In the figure 45, the subject presents a mild-level of apathy. The HeatMap indicates a trend of one-dimensional trajectory for the saccades and the fixations.



**Figure 45.** Temporal and spatial distribution of ETG data for the patient MF002. Left: Temporal distribution of events (Saccades = yellow; Fixation = green; Blink = blue) in 100 Hz then 1Hz sampling. Below: Number of saccades (blue) and fixations (red) per second. Right: Heat map of saccades and fixations; Distribution of saccades and fixations.

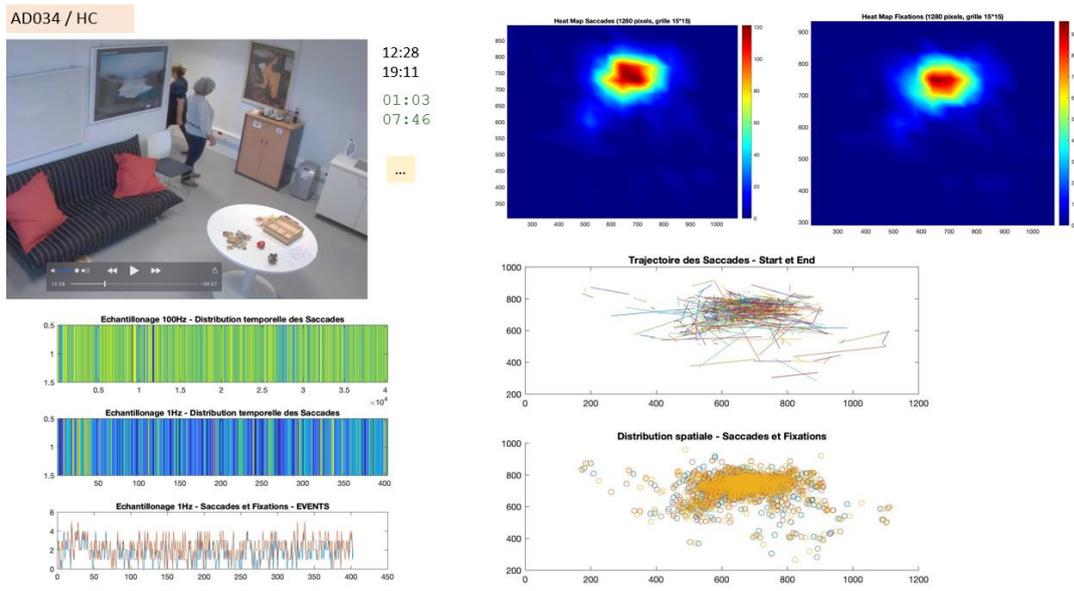
The figure 46 displays the ETG data of a patient presenting a high level of apathy as well as disinhibition. For this patient, the trajectory of saccades and fixations is particularly different from that of the first apathetic patient.

We notice that Heatmaps show trajectories that are not homogeneous between these two patients.



**Figure 46.** Temporal and spatial distribution of ETG data for the patient HM003. Left: Temporal distribution of events (Saccades = yellow; Fixation = green; Blink = blue) in 100 Hz then 1Hz sampling. Below: Number of saccades (blue) and fixations (red) per second. Right: Heat map of saccades and fixations; Distribution of saccades and fixations.

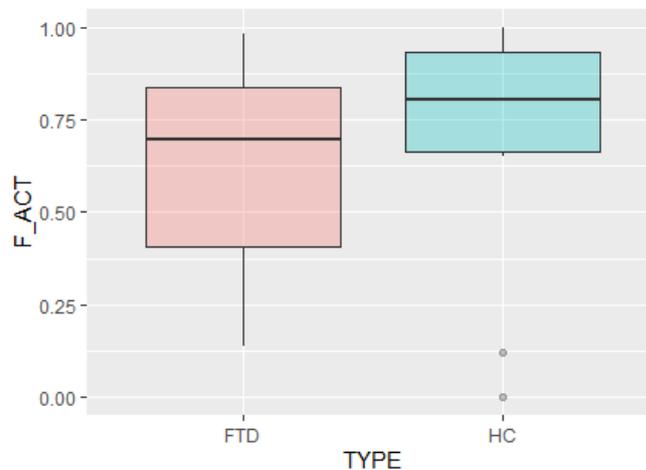
Finally, the ETG data of a healthy volunteer was represented (Figure 47) to highlight the differences with the other two patients FTDa and FTDb. In this case, in fact, we can see from the HeatMap a very homogeneous trend of saccades and fixations, due to their greater ability to remain focused with the gaze on a fixed object, with the intention of carrying out an action.



**Figure 47.** Temporal and spatial distribution of ETG data for the healthy volunteer AD034. Left: Temporal distribution of events (Saccades = yellow; Fixation = green; Blink = blue) in 100 Hz then then 1Hz sampling. Below: Number of saccades (blue) and fixations (red) per second. Right: Heat map of saccades and fixations; Distribution of saccades and fixations

#### 6.5.4. Comparison of activities during the ETG phase

During the ETG phase, the coefficients were calculated as a percentage of the duration of the different activities carried out by the subjects. This analysis was a further marker to make a distinction in the behavior of the two groups of subjects using R software.

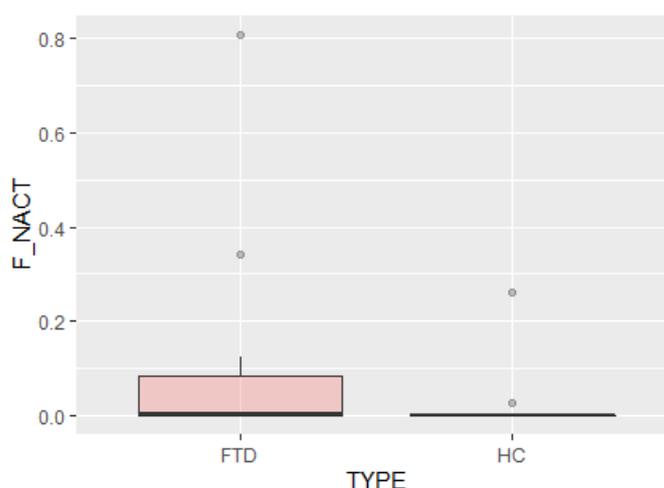


**Figure 48.** Comparison of ACTIVITY percentage during ETG phase between bvFTD patients and healthy volunteers

Figure 48 shows how, when analyzing the boxplots representing the time percentage factors during the ETG phase for the ACTIVITY phase, healthy volunteers present a higher average of bvFTD patients. In addition, patients have a visibly higher variance than healthy volunteers, indicating that healthy volunteers have a more homogeneous and regular activity among themselves, being able to maintain the continuation of an activity towards a goal.

On the other hand, the bvFTD patient ACTIVITY boxplot explains how the behavior of bvFTD patients is rather irregular and uneven, having difficulty in maintaining a fixed activity and achieving a particular goal.

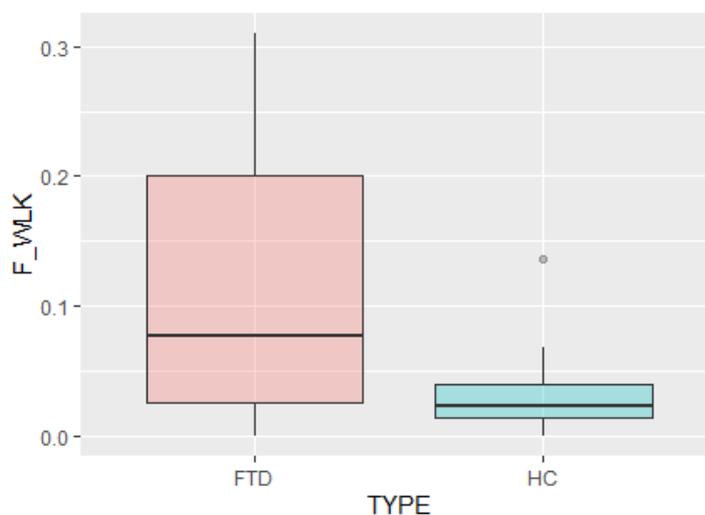
Another significant example is shown by Figure 49 which shows the trend in the percentage time factors of NON-ACTIVITY of healthy volunteers and bvFTD patients. Although the average of bvFTD patients is very low, bvFTD patients have a much larger boxplot than healthy volunteers, who have a virtually non-existent boxplot, with the average tending to zero.



**Figure 49.** Comparison of NON-ACTIVITY percentage during ETG phase between bvFTD patients and healthy volunteers

Healthy volunteers during the ETG phase are always in the process of performing some activity. The last important difference regarding the activities during the ETG phase can be underlined for the WALKING phase, according to which the bvFTD patient group has a rather variable percentage factor trend compared to that of healthy volunteers, which is rather homogeneous and regular.

Figure 50 representing the two boxplots is a further demonstration of our assumptions.



**Figure 50.** Comparison of *ACTIVITY* percentage during ETG phase between bvFTD patients and healthy volunteers

#### 6.5.5. ETG metrics

After calculating several different kinematic metrics from the data extracted from the Eye-tracking phase, the ANOVA test was applied to these metrics in order to identify any differences between FTD patients and healthy volunteers.

An ANOVA test shows a significant difference ( $p < 0.05$ ) in the average duration of fixation, which is higher in bvFTDs than in HCs (Table 20). This longer duration of fixation can be an argument in favor of differentiation between patients and healthy volunteers. This can be interpreted as an increased tendency of bvFTD patients to remain fixated on certain objects without taking action following a certain objective.

As far as the other metrics are concerned, there are no other significant differences and two specific reasons for this have been identified:

The first reason is the heterogeneity of the bvFTD group that we had already observed at a neuropsychological level; moreover, we had information from the medical records on the duration of the disease for some patients (11/14) and the number of years of the disease varies from 1 year to 10 years. Knowing that FTD is part of the DLFT and that the FEF responsible for programming and performing the saccades can be achieved, these data reinforce the

heterogeneity of the bvFTD patient group and may explain why the results of the comparison of oculomotricity metrics are not significant.

The second reason is the poorly controlled nature of the observation condition (almost real situation). To go further in the analysis of this data, it was decided to further control the acquisition context, taking into account the behavior of the subject, and thus segmenting the total observation of 7 minutes into sequences of interest (SOI, Sequence Of Interest).

	<b>HC (n=12)</b>	<b>BvFTD (n=14)</b>	<b>ANOVA</b>	<b>Comparison</b>
<b>Amplitude</b>	2.34-9.76 (5.66)	2.20-11.88 (5.43)	n.s.	
<b>PeakSpeed</b>	113.66-404.93 (215.60)	109.05-395.18 (231.57)	n.s.	
<b>AverageSpeed</b>	46.48-157.71 (89.11)	43.7- 163.81 (94.15)	n.s.	
<b>freqSacn</b>	0.01-0.29 (0.15)	0.02-0.2 (0.11)	n.s.	
<b>freqFixn</b>	0.05-0.82 (0.59)	0.19-0.89 (0.64)	n.s.	
<b>NbSacSec</b>	0.11-3.06 (1.90)	0.51-2.41 (1.46)	n.s.	
<b>NbFixSec</b>	0.39-3.22 (2.38)	1.49-2.67 (2.12)	n.s.	
<b>dm_sac</b>	6.2-12.26 (8.26)	5.8-15.63 (8.78)	n.s.	
<b>dm_fix</b>	15.05-30.38 (24.18)	16.49-69.68 (35.8)	F = 6.6511 p = 0.01647 *	BvFTD > HC (p < 0.05)

*Table 20. Metrics ETG*

### 6.5.6. ETG metrics as a function of SOI

The same analyses were then repeated on different sequences of interest (SOI). The attention was then focused on the following sequences:

- I. Exploration
- II. Reading
- III. Game

First, the metrics were analysed, looking for how much each different condition (SOI) had an effect on it, using the following generalised linear model, in which the variable TYPE represents the group (FTD, HC) and the variable SOI (Explore, Read, Play) represents the behavior of the subject:

$$\text{Variable ETG} \sim \text{SEX} + \text{AGE} + \text{TYPE} * \text{SOI}$$

#### *a) Amplitude and Frequency of Saccades*

It is possible to observe (Figure 51, left) the presence of an effect of the subject's behavior on the amplitude of the saccades, in fact the saccades in the bvFTD group and in the HC group have a greater amplitude in the Exploration condition.

The application of the ANOVA test showed that this difference in amplitude between the two groups was significant ( $p < 0.05$ ). A multiple post-hoc comparison test (Tukey HSD) showed that the difference between the exploration and game conditions was significant ( $p < 0.05$ ), as the subjects (bvFTD and HC combined) show on average a greater amplitude of saccades during the exploration phase of the room compared to a game activity. However, the metrics of the amplitude of saccades cannot distinguish between the two groups bvFTD and HC in the exploration condition.

As for the frequency of saccades, Table 21 shows how the values are higher in the Exploration condition.

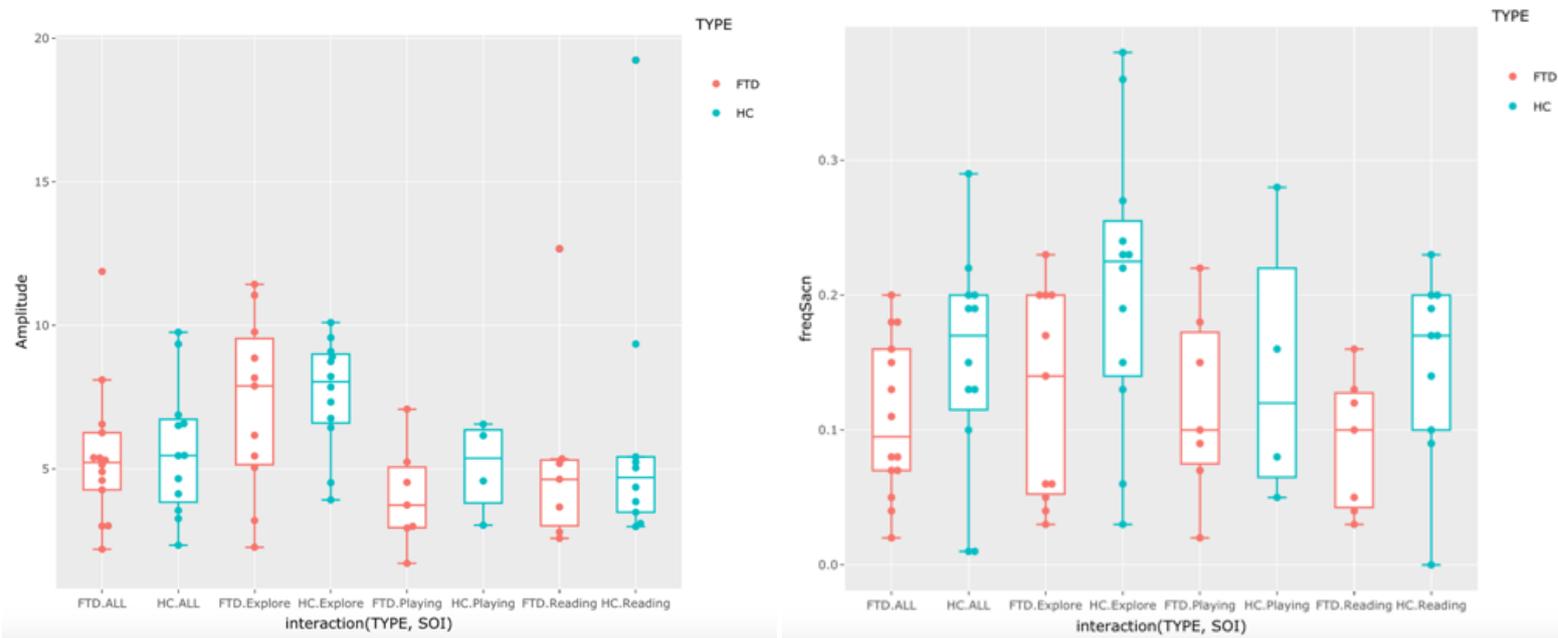


Figure 51. Box plots Amplitude and Frequency of saccades

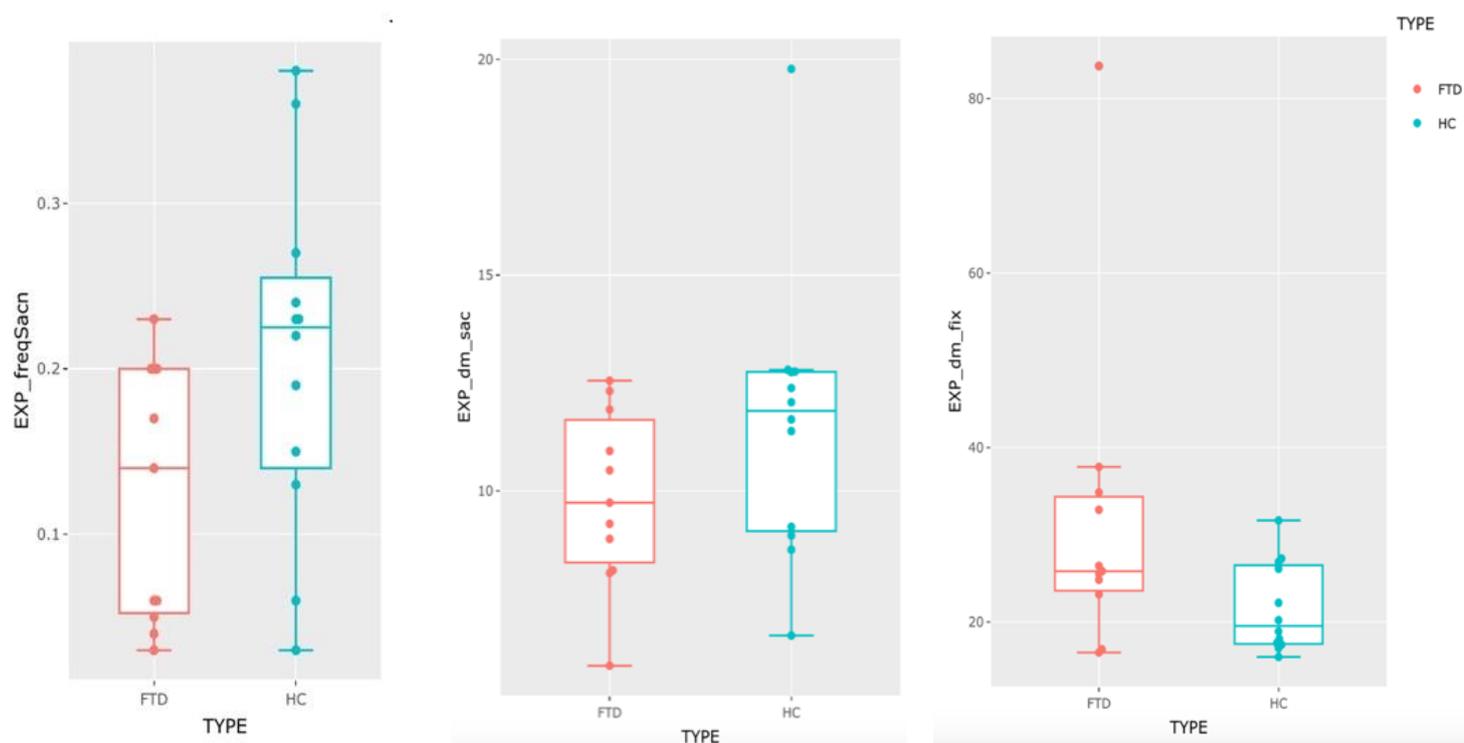
However, no effect due to the group or SOI has been highlighted for the saccades frequency metric. These observations and results led to the analysis of all ETG metrics in the Exploration condition.

*b) ETG metrics in the Exploration condition*

In this condition of exploration, 15 bvFTD patients are considered only 12, as the remaining 3 spend their time exclusively in a game activity (Puzzle or Kapla) without exploring the room. A significant difference in the frequency of saccades was identified (Table 7), as demonstrated by the ANOVA test ( $p < 0.05$ ). HC subjects have on average a higher frequency of saccades during room exploration than bvFTD patients. This result confirms one of our hypotheses: the initiation of voluntary eye movements is reduced in subjects with bvFTD, e.g. with a lower frequency of saccades, leading to a decrease in the ability to visually explore a new environment.

No other ETG metrics in the exploration condition demonstrated a significant difference between bvFTD patients and healthy volunteers.

In conclusion, it can be said that the ocular behavior of bvFTD patients is characterized by rarer and shorter saccades than healthy subjects, as well as longer fixation times.



**Figure 52.** On the left, box plots representing the frequency of saccades in HC (blue) and bvFTD (red) in Exploration condition. In the centre, box plots representing the average duration of a saccade in HC (blue) and bvFTD (red) in Exploration condition. On the right, box plots representing the average duration of a fixation in HC (blue) and bvFTD (red) in Exploration condition.

	HC (n=12)	bvFTD (n=15)	ANOVA	Comparison
<b>EXP_Amplitude</b>	3.92-10.10 (7.62)	2.27-11.43 (7.21)	n.s.	
<b>EXP_PeakSpeed</b>	178.49-504.74 (271.66)	102.47-390.59 (246.10)	n.s.	
<b>EXP_AverageSpeed</b>	45.77-172.89 (105.65)	40.31- 170.04 (99.77)	n.s.	
<b>EXP_freqSacn</b>	0.03-0.38 (0.21)	0.03-0.23 (0.12)	F = 4.4455 p = 0.04718 *	HC > BvFTD (p < 0.05)
<b>EXP_freqFixn</b>	0.13-0.85 (0.52)	0.21-0.8 (0.53)	n.s.	
<b>EXP_NbSacSec</b>	0.39-3.17 (1.87)	0.57-2.87 (1.46)	n.s.	
<b>EXP_NbFixSec</b>	1.47-3.32 (2.42)	1.46-3.03 (2.1)	n.s.	

EXP_dm_sac	6.64-19.78 (11.58)	5.94-12.55 (9.83)	F = 2.3026 p = 0.1441	
EXP_dm_fix	15.95-31.61 (21.57)	16.46-83.74 (31.64)	F = 3.2845 p = 0.08426	BvFTD > HC (p < 0.05)

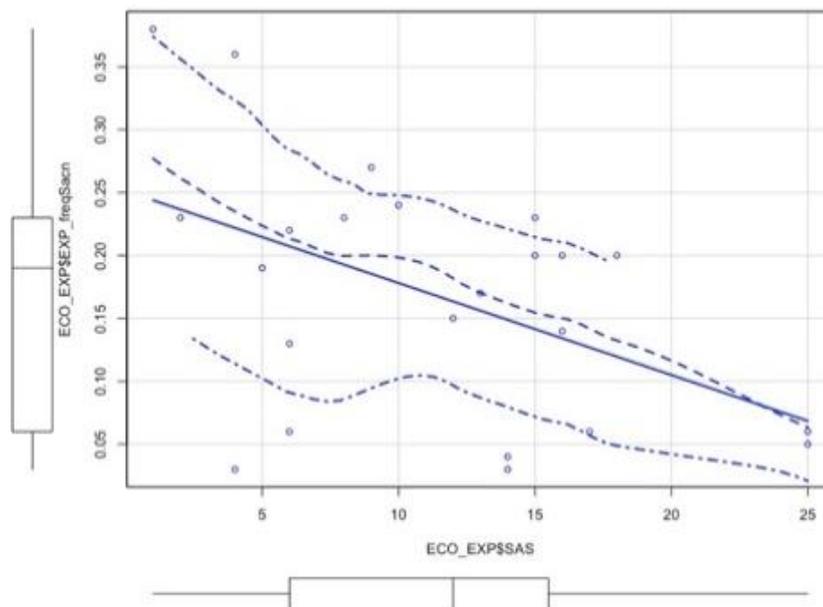
**Table 21.** ETG metrics in EXPLORATION condition

*c) Effect of apathy level on ETG metrics in condition Exploration*

To complete the analysis, the apathy score (measured by the STARKSTEIN scale) was examined to see if it had an influence on the ETG metric in the Exploration condition.

The ANOVA test showed the presence of an effect on EXP\_freqSacn metric (p = 0.01834 \*), EXP\_NbSacSec metric (p = 0.08831) and EXP\_NbFixSec (p = 0.05803).

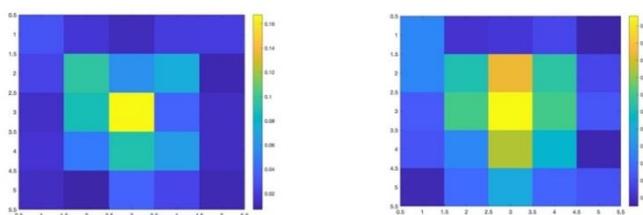
In addition, the analyses show a correlation (r=0.39, p=0.07) between the clinical level of apathy (SAS) and the frequency of saccades, which decreases as the apathy score is higher (Figure 53).



**Figure 53.** Correlation between the level of apathy and the frequency of saccades.

### 6.5.7. Patterns of spatial distribution of saccades

As a final analysis of the ETG phase, an average Heatmap per group was derived, resulting in an average model for HCs and one for bvFTDs. It can be noted that the visual model indicates a wider distribution of visual gaze for HCs than for patients who obviously perform a smaller visual exploration (Figure 54).



**Figure 54.** Heatmap representing the distribution of the gaze on a 5x5 grid. On the left, average Heatmap for the bvFTD group; on the right, average Heatmap for the HC group.

## 6.6. MRI IMAGE ANALYSIS

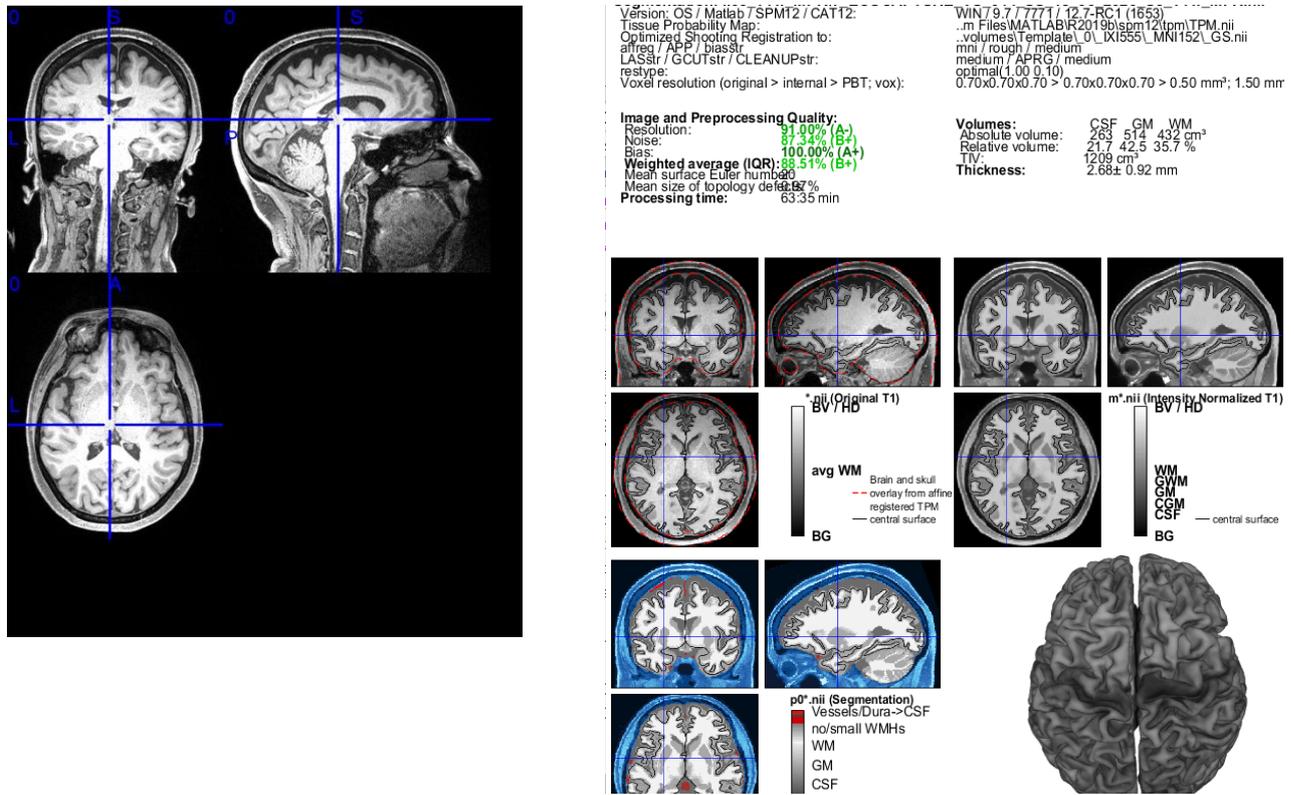
In order to have an all-round view of the degree of advancement of bvFTD and consequently of the estimated level of apathy, with the classification and regression techniques applied, the images obtained from the magnetic resonance imaging (MRI) examination to which all subjects participating in the program were subjected were analyzed.

This analysis was carried out using the "SPM12" software, which makes it possible to analyse brain imaging sequences and to perform a segmentation of the MRI images, extracting some very useful statistical data to confirm the hypotheses of this work.

In particular, thanks to the use of a particular toolbox called "CAT" which has the possibility to provide a computational anatomy using some morphometric methods. This toolbox uses internal interpolation to provide more reliable results even with low resolution images and anisotropic spatial resolutions.

One of these methods allows the measurement of cortical thickness and reconstruction of the central surface, using tissue segmentation to estimate the distance of white matter (WM). This method projects local maxima to other grey matter voxels using a neighborhood relationship

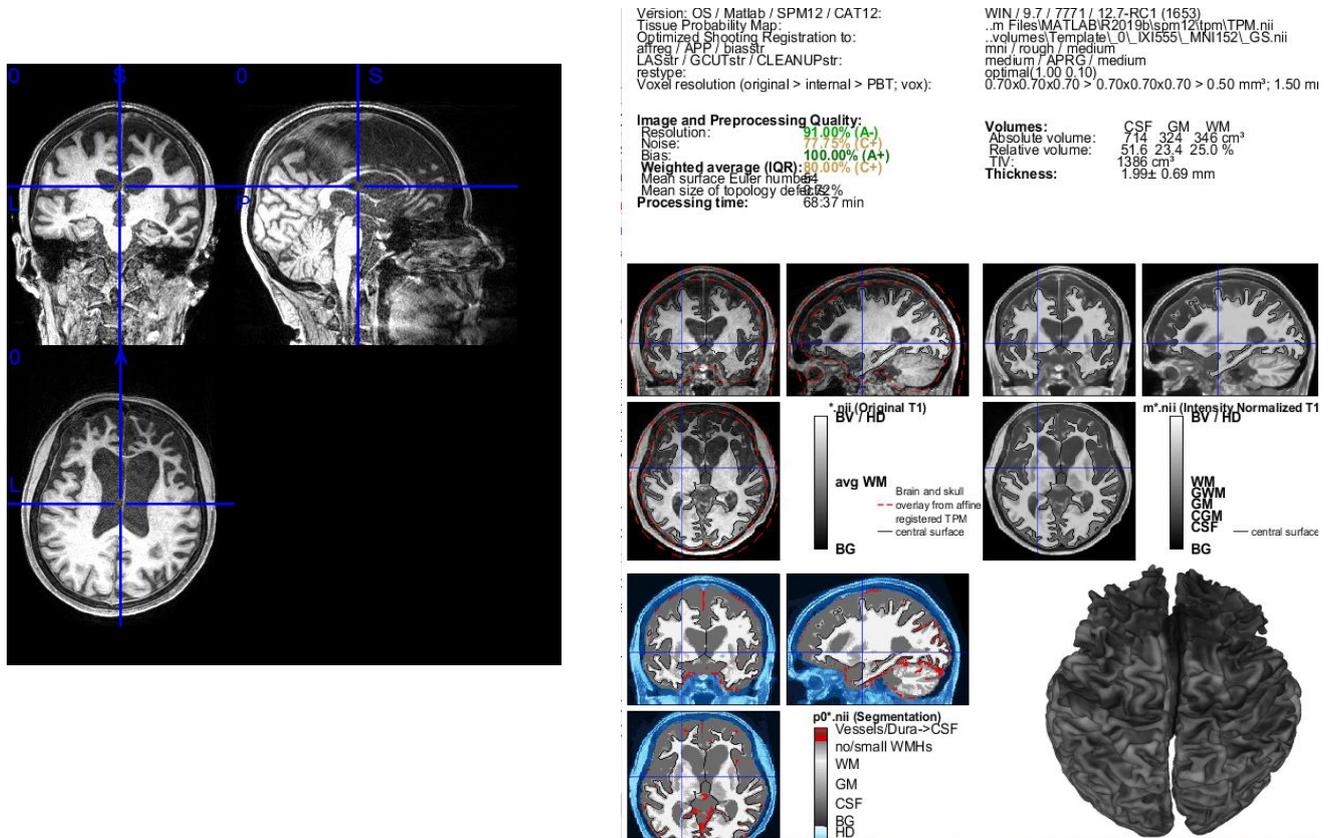
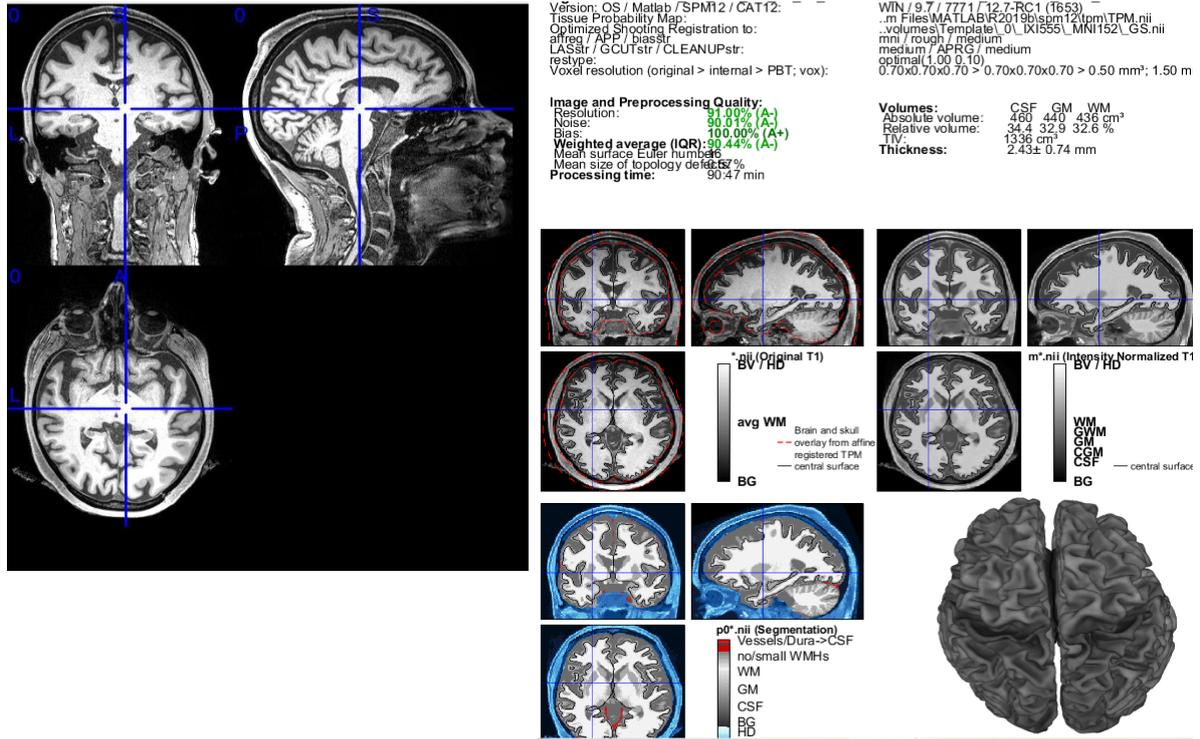
described by the WM distance. Analysis was applied to bvFTD patients MRI data and HC MRI data (Figures 55-57).



**Figure 55.** *Left:* Frontal plane, sagittal plane and transversal plane of HC brain. *Right:* CAT algorithm segmentation for HC.

The MRI examination of a healthy volunteer (Figure 55, left) is viewed from three different axes. Figure 55 (right) shows the result of the segmentation performed by the software "SPM12" which provides as a result the estimate of the partial volume of white and grey matter and consequently the cortical thickness.

The same MRI processing was applied and reported in Figures 56 and 57 for two apathetic patients. As is clearly visible from the MRI images, the first patient has a higher level of atrophy: a decrease in cortical thickness, a decrease in the amount of grey matter, may impact the severity of apathy. Compared to the HC cortical thickness (2.68 mm), the two patients FTDa and FTDb present a lower thickness (2.43 mm and 1.99 mm respectively), which reflects the degree of atrophy of the fronto-temporal lobe and could explain the level of apathy.



## VII. MULTIVARIATE LINEAR REGRESSION

Multivariate linear regression works in a similar way to the linear model, but uses more dependent and independent variables, thus having more data to process.

The objective of multivariate regression is to measure the degree of correlation of an independent variable with other dependent variables; independent variables are called "predictors" and dependent variables are called "responses".

Multivariate regression is therefore based on general linear models, used to predict the behavior of some dependent variables (responses) in association with changes in the independent variables (predictors).

The form with which we can express the multivariate linear regression model is as follows:

$$Y_i = \beta_0 + \beta_1 x_i^{(1)} + \beta_2 x_i^{(2)} + \dots + \beta_n x_i^{(n)}$$

With:

- $Y_i$  = estimate of the  $i$ -th component of the dependent variable  $y$
- $n$  = number of independent variables
- $x_i^{(n)}$  =  $i$ -th component of  $n$ -th independent characteristic variable
- $\beta$  = represents the various regression coefficients

$Y$ ,  $x$  and  $\beta$  represent matrices, as there are  $n$  independent variables and  $m$  dependent variables.

To express the level of reliability of the model, the cost function is used, which in a multivariate regression model can be expressed as a vector and resembles that of the mean square error:

$$E(\beta_0, \beta_1, \beta_2, \dots, \beta_n) = \frac{1}{2m} \sum (h_{\beta}(x^{(i)}) - y^{(i)})^2$$

As a difference there are  $m$  dependent variables and  $y$  are the data foreseen by the  $i$ -th dependent variable. The vector  $h$  represents the value observed for each dependent variable. From the sum of each of these high differences squared and dividing by  $2m$ , the value of the cost function for the multivariate linear regression model is calculated.

The objective is the minimization of this function, which passes through the estimation of Beta values and increases as much as possible the level of accuracy of the model forecasts.

### 7.1. MULTIVARIATE DISTANCE MATRIX REGRESSION

After the classification and the various analyses of the data, a regression algorithm of the neuropsychological data has been applied so that it is possible to predict the values of some variables of a subject, knowing others.

The technique applied is the multivariate distance matrix regression (MDMR) and allows to relate a number  $N$  of independent variables collected on  $M$  individuals, where  $N > M$  [26]. Its functioning is based on the distances between pairs of individuals with respect to the  $N$  variables, with which the matrix containing the distances between the variables ( $M \times M$ ) is constructed, thanks to which it is possible to test the association and similarity between the independent variables. This method is rooted in traditional models and the first to use it were McArdle and Anderson (2001).

The similarities and differences are used to construct the distance matrix and therefore MDMR has similarities with some data reduction strategies, although by directly associating all the variables, it does not reduce the amount of data [27].

This regressive approach is often used as a clustering technique, since it is based on distance and similarity measurements. In this case the aim of this method was to predict the behavior of dependent variables based on the values of the independent variables.

#### 7.1.1 Application for neuropsychological data

The regression algorithm has been used using Matlab, using the "mvregress" routine which allows the application of MDMR by calculating a matrix of distance between the independent variables [28].

The final objective was to predict the value of some of these variables.

As a matrix of the dependent variables (answers)  $Y$ , i.e. the variables whose values are intended to be predicted, the SAS (clinical level of apathy) values of each patient were chosen.

$$Y = [SAS]$$

As a matrix of the independent variables X all other neuropsychological variables were used for each patient:

$$X = [ \text{SEX AGE SCL MMSE MATTIS DAS\_EXE DAS\_EMO DAS\_INI HAD\_ANXIETY HAD\_DEPRESSION BREF HAYL\_A HAYL\_B HAYL\_ERR MINI\_SEA} ]$$

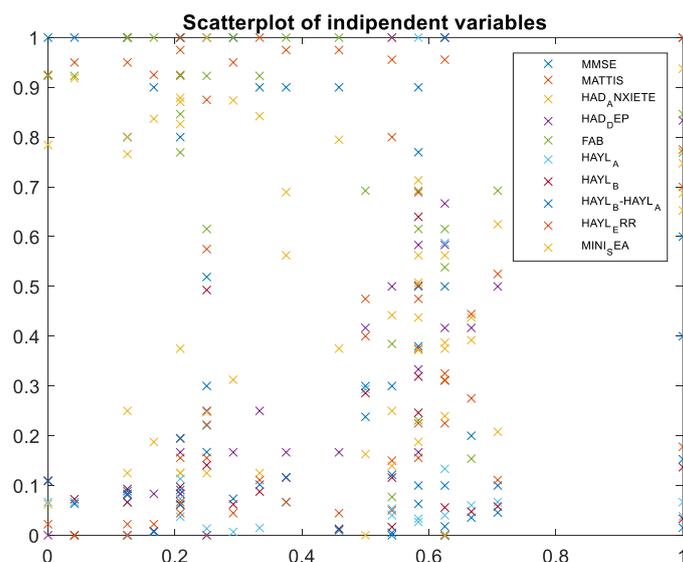
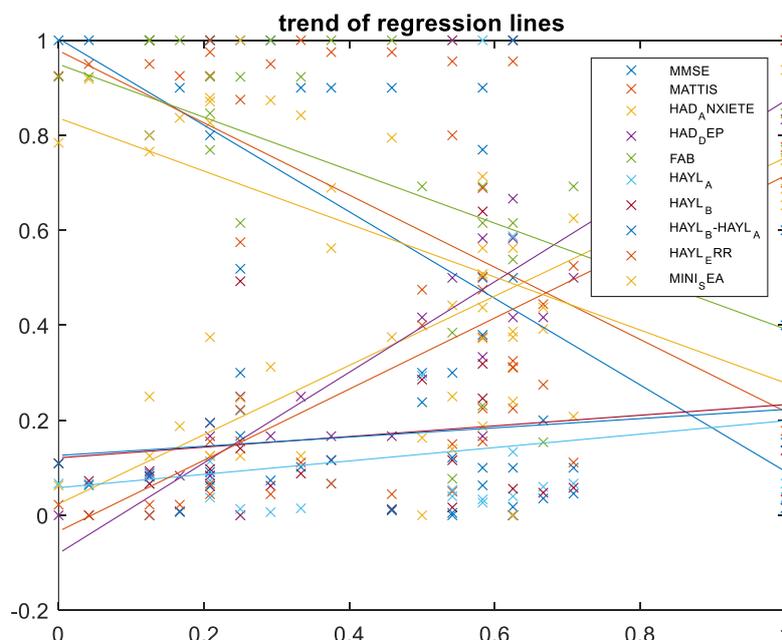


Figure 58. Scatter plot of independent variables

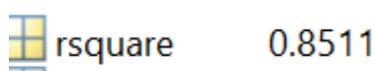
The independent variables have been normalized according to the maximum value and represented by a scatter plot to visualize their trend along the Cartesian plane.

In order to be able to predict the behavior and therefore estimate the value of the dependent variable SAS for each patient, the straight line representing the trend has been fitted. The lines have been very useful for the calculation of the sigma matrix, the matrix of the variances between the variables, based on the  $\beta$  matrix of the regression coefficients..



**Figure 59.** Trend of regression lines of each independent variable

Matlab's algorithm has also provided the tolerance and reliability coefficient  $R^2$  which has a range of values from 0 to 1 and expresses how reliable the regressive model is for the dataset used.



**Figure 60.** Confidence coefficient value of regression model

In this case the  $R^2$  coefficient is higher than 0.85 and therefore it can be concluded that the regressive model is pretty reliable and so we can estimate SAS values of a patient, knowing other neuropsychological data.

## VIII. CONCLUSIONS

Analysis of neuropsychological data, video-base behavioral data, sensor-based data (acceleration), eye tracking data and MRI data identify a set of relevant metrics that discriminate bvFTD patients from healthy controls.

Due to the particular health conditions in the year 2020, it was not possible to carry out all the desired analyses, especially with regard to the spatial distribution of the participants' binocular gaze, and the MRI data. However, we have been able to report some results:

1/ The time-series behavioral matrices of dummy-codes, present in a differentiated way, behavior for the HC and for bvFTD patients. This method shows that HC and patients present a specific behavioral pattern, particularly during the very first minutes they entered and discovered the room. Facing with a new environment, HC first explored it for a short period of time and then engaged in sustained activity. In contrast, bvFTD patients were characterized by greater inactivity and less exploration/activity than HC. This exploration deficit under ecological is a behavioral indicator of apathy in frontotemporal dementia.

2/ From the graph representing the trend of acceleration average in the ETG phase, we observe how bvFTD patients present a rather irregular trend of acceleration average, compared to HC (the right of the red bar) that present a more regular and more uniform acceleration average.

3/ In addition, eye tracking data also identified some metrics that differentiate bvFTD patients from healthy volunteers. The processing and visual representation of the ocular event (saccades, fixations) from ETG data, highlight:

- The temporal distribution of saccades
- The spatial distribution of saccades
- The dispersion of the gaze through Heatmap

Analysis of the HeatMap showed that the spatial distribution of the gaze of healthy volunteers was more homogeneous than that of patients. In HC, the gaze distribution appeared as a very homogeneous trend of saccades and fixations, due to their greater ability to remain focused with the gaze on a fixed object, with the intention of carrying out an action. This greater homogeneity in space, correlated with a higher saccadic frequency in healthy volunteers, giving them a better

ability to explore. Furthermore, the spatial distribution of gaze is similar from one healthy volunteer to another, while each gaze distribution has its own specificity compared to the others in bvFTD patients. Some subjects show a one-dimensional pattern (all saccades seem to go in the same direction), while others show a multidimensional pattern (saccades are performed in many directions).

Moreover, we showed that the ocular behavior of bvFTD patients was characterized by rarer and shorter saccades than healthy subjects, as well as longer fixations. This result confirms one of our hypotheses: The initiation of voluntary eye movements is reduced in subjects with bvFTD, e.g. with a lower frequency of saccades, leading to a decrease in the ability to visually explore a new environment.

4/ The MRI processing applied for two apathetic patients and an HC, showed the first patient had a higher level of atrophy: a decrease in cortical thickness, a decrease in the amount of grey matter, Compared to the HC cortical thickness, the two patients FTDa and FTDb presented a lower thickness linked to the degree of atrophy of the fronto-temporal lobe and could explain the level of apathy.

5/ The unsupervised learning algorithms applied on the neuropsychological data, separated the subjects into three groups, HC, FTDa, and FTDb, according level of apathy severity and/or disinhibition. Thanks to a multivariate distance matrix regressing model, it was possible to estimate the level of apathy (SAS value) of a patient, knowing other neuropsychological data.

It would therefore be interesting to develop artificial intelligence tools to also deeply classify and identify these models and compare different sub-groups of bvFTD patients. This would allow to test the existence of the three forms of apathy: executive, motivational and initiation. These behavioral and sensor-based markers would be correlate with imaging makers to contribute to the knowledge of the neural basis of apathy and goal-directed behavior.

However, these analyses only covered 12 HC subjects and 15 bvFTD patients, so it seems necessary to extend the analysis to a larger number of cases to validate the robustness of the above metrics and to further explore the quantitative assessment scale for apathy. In fact, the

## *CONCLUSIONS*

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ECOCAPTURE project is evolving in this direction, as it aims to extend to 75 patients and 60 healthy volunteers, in order to carry out a more in-depth analysis of the data and strengthen the metrics that contribute to the behavioral signature of apathy.



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