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## **A temporal classification method based on behavior time series data in patients with behavioral variant of frontotemporal dementia and apathy**

Caroline Peltier, François-Xavier Lejeune, Lars G.T. Jorgensen, Armelle Rametti-Lacroux, Delphine Tanguy, Valérie Godefroy, David Bendetowicz, Guilhem Carle, Emmanuel Cognat, Stéphanie Bombois, et al.

### ► To cite this version:

Caroline Peltier, François-Xavier Lejeune, Lars G.T. Jorgensen, Armelle Rametti-Lacroux, Delphine Tanguy, et al.. A temporal classification method based on behavior time series data in patients with behavioral variant of frontotemporal dementia and apathy. *Journal of Neuroscience Methods*, 2022, 376, pp.109625. 10.1016/j.jneumeth.2022.109625 . hal-03699572

**HAL Id: hal-03699572**

**<https://hal.sorbonne-universite.fr/hal-03699572>**

Submitted on 22 Jul 2024

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## Research Paper

### Title.

A temporal classification method based on behavior time series data in patients with behavioral variant of frontotemporal dementia and apathy.

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# 1 Introduction

## 2 1. Behavioral variant frontotemporal dementia (bvFTD) and apathy

3 Apathy is a common behavioral syndrome that occurs across a wide range of neurological and  
4 psychiatric disorders.<sup>1,2</sup> It is the most common neuropsychiatric syndrome (NPS) associated with  
5 behavioral variant frontotemporal dementia (bvFTD), but it is also highly prevalent in other  
6 neurodegenerative conditions.<sup>2,3</sup> BvFTD is an early-onset neurodegenerative disease resulting from  
7 frontotemporal lobar degeneration,<sup>3</sup> and it is characterized by a progressive deterioration of  
8 personality, social conduct and cognition.<sup>4</sup> BvFTD is a good model for studying apathy because  
9 apathy is one of the core features of bvFTD,<sup>5</sup> and it remains almost constant throughout the  
10 disease.<sup>6</sup> In 2011, the International bvFTD Criteria Consortium (FTDC) developed revised  
11 guidelines for the diagnosis of bvFTD, wherein bvFTD is a syndrome defined by a set of clinical  
12 (behavioral and cognitive) criteria: disinhibition, apathy/inertia, loss of empathy,  
13 perseverative/compulsive behaviors, hyperorality and a dysexecutive neuropsychological profile.<sup>4</sup>

14 Traditionally, apathy has been viewed as a symptom indicating loss of interest or emotions.  
15 In 1990, in a highly influential conceptual framework, Marin defined apathy as “diminished  
16 motivation not attributable to diminished level of consciousness, cognitive impairment, or  
17 emotional distress”.<sup>7</sup> Marin (1991), in his paper entitled “Apathy: a neuropsychiatric syndrome”  
18 introduced a major evolution of the concept of apathy. He suggested that neuropsychiatric disorders  
19 also produce a syndrome of apathy and proposed diagnostic criteria for the syndrome of apathy  
20 (i.e., a syndrome of primary motivational loss, that is loss of motivation not attributable to  
21 emotional distress, intellectual impairment, or diminished level of consciousness) on the basis of its  
22 distinction from the overt behavioral, cognitive, and emotional concomitants of goal-directed  
23 behavior.<sup>8</sup> However, according Marin (1991), both the symptom and the syndrome of apathy are of  
24 conceptual interest. In 2001, Starkstein et al. operationalized Marin’s criteria into a set of diagnostic  
25 criteria for apathy,<sup>9</sup> and on the basis of Marin’s Apathy Evaluation Scale,<sup>10</sup> they designed a  
26 simplified 14-item scale (Starkstein Apathy Scale) that can be used with patients and caregivers.<sup>11</sup>  
27 In 2000, Stuss et al. argued that apathy cannot be clinically defined as a lack of motivation because  
28 the assessment of motivation is problematic and usually requires inferences based on observations  
29 of affect or behavior.<sup>12</sup> They suggested that apathy is best characterized in behavioral terms as “an  
30 absence of responsiveness to stimuli - internal or external - as demonstrated by a lack of self-  
31 initiated action”.<sup>12</sup> According to the authors, there are many advantages to this definition: (1) it  
32 provides objective behavioral measurements; (2) apathy is not a singly definable state or a single

33 syndrome; and (3) apathy can be divided into separable types (states). Stuss’s conceptualization of  
34 apathy states (apathetic behaviors) is derived from the model of frontal lobe function developed by  
35 Stuss and colleagues.<sup>13</sup> The authors emphasized: (i) emotional apathy, i.e., lack of concern and  
36 limbic affective input as reward sensitivity; (ii) cognitive apathy, i.e., absence of initiated behavior  
37 due to executive dysfunction as planning; and (iii) behavioral apathy, i.e., diminished self-initiated  
38 actions).<sup>12</sup>

39 In 2006, in another influential theoretical framework, Levy and Dubois refined the definition  
40 of apathy to “the quantitative reduction of self-generated voluntary and purposeful behaviors”.<sup>14</sup>  
41 Consequently, the authors argued that, first, apathy is an *observable state* that can subsequently be  
42 quantified; second, apathy is a pathology of voluntary action or goal-directed behavior (GDB); and  
43 third, the underlying mechanisms responsible for apathy are related to dysfunctions of the  
44 elaboration, execution or control of GDB.<sup>14</sup> Within neuroscience, GDB is understood as a set of  
45 related processes by which an internal state is translated, through action, into the attainment of a  
46 goal.<sup>15</sup> Levy and Dubois proposed an apathy model, partly aligned with previous  
47 conceptualizations, and they emphasized the multifactorial nature of apathy by defining three  
48 subtypes based on the impairment of distinct prefrontal cortex-basal ganglia circuits: (1) emotional-  
49 affective apathy refers to an inability to associate affective and emotional signals with ongoing and  
50 forthcoming behaviors and manifests as indifference or flat affect (unconcern); (2) cognitive apathy  
51 relates to impaired elaboration of plans for action; and (3) autoactivation apathy refers to difficulties  
52 in initiating the motor program necessary to complete the behavior.<sup>14</sup> Recently, the criteria for  
53 apathy were revised by an international consensus group.<sup>2</sup> The new diagnostic criteria propose that:  
54 (1) apathy is defined as “a quantitative reduction of goal-directed activity in comparison to the  
55 patient’s previous level of functioning”; and (2) apathy is a persistent state, the symptoms of which  
56 should be observed in at least two of the following three dimensions: behavior/cognition; emotion  
57 (including both spontaneous emotions and emotions in response to the environment/others); and  
58 social interaction (including both spontaneous social initiative and environment/other-stimulated  
59 social interaction).<sup>2</sup>

60 The assessment and measurement of apathy are crucial in clinical practice, as well as in  
61 research settings. Apathy is commonly assessed using a variety of instruments, including diagnostic  
62 criteria-based clinical interviews and validated assessment scales, based on patient (self-rated)  
63 and/or informant reports.<sup>16,17</sup> While many apathy scales are available, several limits have been  
64 identified. First, these scales are biased by the subjective evaluation of the patient or his or her  
65 relatives, and important differences in quotations can be noted between patients and caregivers,<sup>18</sup>

66 especially in neurological diseases with anosognosia, such as bvFTD. Second, the psychometric  
67 properties of the scales can vary across different populations, and they provide only subjective  
68 measurements of the patient's internal state, thoughts and past activities.<sup>17</sup> Finally, although some  
69 scales, such as the Dimensional Apathy Scale (DAS),<sup>19</sup> aim to differentiate the different forms of  
70 apathy, future research should address the ability to distinguish subtypes of apathy.

71 Thus, a challenging issue is the need to measure apathy objectively, reflecting the type of  
72 apathetic behavior (i.e., the form of apathy) investigated. To address this issue, direct behavioral  
73 observation in the natural environment or in simulated settings under more controlled conditions  
74 and structured scenarios, as well as behavioral sensing (sensor, video), is a promising method and  
75 tool. Burgess and Stuss,<sup>20</sup> reviewing fifty years of prefrontal cortex research and their impact on  
76 assessment, stated that “tests that mimic naturalistic situations may be just as effective in terms of  
77 time-effectiveness, discrimination power, specificity, sensitivity, and ease of administration (and  
78 sometimes perhaps more so) as those that do not”.<sup>20</sup> The group of experts in the domain of apathy in  
79 brain disorders who revised the diagnostic criteria for apathy also suggested appropriate and  
80 updated tools that can be employed to assess apathy: (1) a number of clinical scales; and (2) new  
81 information and communications technologies (ICTs),<sup>2</sup> due to the emerging evidence that “new ICT  
82 approaches could provide clinicians with valuable additional information in terms of assessment,  
83 and therefore more accurate diagnosis of apathy”.<sup>21</sup>

84 In line with these considerations, in a previous work,<sup>22</sup> we built an ecological framework  
85 under controlled conditions and a structured scenario (ECOCAPTURE, FRONTlab, ICM) designed  
86 to identify and measure behavior and/or behavioral disorders to obtain objective and quantitative  
87 measurements for assessing neuropsychiatric symptoms, such as apathy<sup>22</sup> and disinhibition,<sup>23</sup> given  
88 the limitations in measuring these behaviors using questionnaires and scales administered to  
89 patients or caregivers. In this study, we used the ECOCAPTURE protocol to investigate behavior in  
90 bvFTD patients under ecological conditions (a waiting room) while they freely explored a novel  
91 environment, and we examined individuals performing a continuous stream of behavior (behavior  
92 flow) over a 7-minute testing session (a part of the ECOCAPTURE scenario), in order to contribute  
93 to the identification of apathy-like behaviors and thus the characterization of apathy.

94

## 95 **2. Direct behavioral observation and the ethological approach**

96 Ethology, the “biology of behavior”,<sup>24</sup> is a scientific discipline stemming from biology that  
97 studies the behavior of animals in the natural environment. Human ethology, founded by Eibl-

98 Eibesfeldt,<sup>24,25</sup> was established on the basis of classical zoo-ethology in connection with Lorenz's  
99 work,<sup>26,27</sup> and it has become an integral part of modern ethology. In our paper, the basic concepts,  
100 methods and tools related to ethology are used in relation to human ethology. The method of direct  
101 observation is the necessary link between laboratory research and "real-world" behavior and a key  
102 way to obtain more accurate, more objective information about behavior.<sup>28</sup> This method requires  
103 that the observer has a well-formulated research question and that he or her has a preliminary  
104 catalog of behaviors of interest called an ethogram. Ethograms are directories of species-typical  
105 behaviors observable under specific conditions, usually grouped into categories according to the  
106 type of behavior. Theoretically, in a specific category, all behaviors should be mutually exclusive  
107 (e.g., standing/sitting or activity/nonactivity): "Ethologists typically use two types of descriptions  
108 when constructing ethograms; *motor patterns* objectively describe physical movements made by the  
109 animal, while descriptions by consequence are *behaviors* defined in relation to the animal's  
110 environment".<sup>29</sup> Indeed, it is not the brain alone that produces behavior but rather its interaction  
111 with an even more complex and changing environment.<sup>30</sup>

112 The observer can consider behavior from different scales (for example, performing an  
113 activity is composed of a sequence of actions, including initiating the activity and maintaining the  
114 activity, or walking is a set of repetitive movements) and chooses the most effective scales of  
115 analysis to measure behavior. The complexity of behavior allows for many alternative  
116 segmentations depending on the level of information selected.<sup>31</sup> Thus, the behavior is broken up  
117 into units called behavior units or action patterns. Behaviors (or action patterns) are discrete,  
118 repeatable, and identifiable acts.<sup>29</sup> Once the behaviors of interest are defined, measurements are  
119 obtained in carefully selected and defined behavior units.<sup>32</sup>

120 Sampling decisions are another key point for behavioral data collection, especially with  
121 regard to the scheduling of session onsets (e.g., a sample session might be scheduled to begin at a  
122 predetermined time) or session terminations (e.g., after a fixed period). *Behavior continuous*  
123 *sampling* means that the observer watches the subject and records each occurrence of a particular  
124 behavior (and describes the context in which it occurs) for the entire duration of the sample  
125 period.<sup>33</sup> The *behavior continuous sampling* method generates accurate frequency and duration data  
126 through continuous recording, and it is considered the gold standard method.<sup>28,34</sup> Another parameter  
127 to consider in selecting a sampling method is the duration of the behavior (event or state); indeed,  
128 behavior can be regarded either as instantaneous events or as states having an appreciable duration,  
129 and this choice depends upon the questions about the behavior of interest.<sup>28</sup> Another parameter is  
130 the desired scale of measurement (nominal, ordinal, interval, or ratio).<sup>34</sup> Thus, the observer records

131 the number of acts or the amount of time for which the behaviors are performed. An alternative  
132 method is to record action patterns in the order in which they occur, creating a sequence of events to  
133 produce a kinematic diagram. A kinematic diagram (or flow diagram or kinematic graph) provides  
134 an excellent overview of behavioral sequences (i.e., the flow of the behavior)<sup>35</sup> and is useful for  
135 illustrating transitions between behaviors.<sup>32</sup>

136

### 137 **3. Toward a method with behavioral kinetics**

138 As noted by Lehner, “Animals are always behaving. They perform a continuous stream of  
139 behavior from the moment when movement can first be detected in the embryo until their death”.<sup>32</sup>  
140 In this study, instead of focusing on the behavioral sequence and/or the transitions between  
141 behaviors, our method tracked the flow of each specific behavior of interest and considered the  
142 temporal structure of behavioral data. Thus, each overt behavior was considered a signal (i.e., a set  
143 of values ordered by time) during a period of interest, the state changes of which could be analyzed.  
144 Since a signal is by definition a type of time series, the subjects’ behavior data were transformed  
145 into behavior time series data. Therefore, in the rest of the paper, we use mathematical terms to  
146 describe the techniques and algorithms of mathematical time series analysis.

147 The objective of this paper is to present an approach considering behavioral kinetics to  
148 assess behavior in bvFTD patients and identify behavioral patterns contributing to the signature  
149 symptom of apathy. We aimed to construct a new behavior analysis method, called *ECOCAPTURE*  
150 *kinetics*, using temporal classification for behavior time series data analysis.

151 Time series are encountered in many scientific domains, and a large number of time series  
152 classification (TSC) methods and algorithms have been proposed, which were reviewed in Bagnall  
153 et al.<sup>36</sup> and Ismail Fawaz et al.<sup>37</sup>. A classifier is an algorithm that maps the input data to a specific  
154 category (i.e., assigns a class label to a data input). TSC is different from the traditional  
155 classification problem because the attributes in a time series are ordered. Bagnall et al.<sup>36</sup> classified  
156 TSC algorithms into categories, depending on the strategy type based on the period studied (*whole*  
157 *series* or *intervals* of the series), the signal characteristics (the presence or absence of short patterns  
158 or their frequency count), the choice of distances (e.g., *elastic* distance measures) and the use of  
159 *model-based* algorithms for measuring similarities between series. Moreover, two or more of the  
160 above approaches could be combined into a single classifier.

161 In the following, we illustrate some popular classifiers. Two series can be compared either  
162 as a vector or by a distance measure (the Euclidian distance calculation to all points in the dataset),



163 but to compensate for potential localized misalignments between series, the classifiers use elastic  
164 distance measures. For example, dynamic time warping (DTW, also called elastic matching) is an  
165 effective method for measuring the similarity between two time series, which can vary in speed  
166 (e.g., similarities in walking could be detected using DTW, even if one person was walking faster  
167 than the other). In their review, Bagnall et al.<sup>36</sup> claimed that TSC papers in the datamining literature  
168 have cited DTW as the benchmark for comparison. The nearest neighbor (NN) classifier assigns a  
169 time series to the class of its closest neighbor in the feature space using Euclidian distance. One of  
170 the most popular and traditional TSC approaches is the use of an NN classifier coupled with an  
171 elastic distance function.<sup>38</sup>

172 To develop our classifier, we retained a nonelastic Euclidian metric, combined with a  
173 convolutional approach aiming to take into account the neighborhood . We hypothesized that, after  
174 developing our new temporal classification method that inputs behavior time series data (subjects'  
175 behavior flow), we would classify bvFTD patients according to their behavioral kinetics and that  
176 these subgroups would be differentially associated with apathy and other neuropsychological  
177 features and thus would identify specific behavior patterns contributing to the behavioral signature  
178 of apathy. This approach can be extended to any behavioral study encoding time, and an R package  
179 is available as open-source software (OSS).

180

## 181 **Materials and methods**

### 182 **1. The ECOCAPTURE ethological and ecological approach**

#### 183 **1.1 The ECOCAPTURE paradigm**

184 The ECOCAPTURE paradigm mimics a naturalistic situation (i.e., waiting comfortably in a  
185 waiting room), and the behavioral assessment of apathy in participants was driven by a 45-minute  
186 controlled scenario. The experiments took place on an experimental platform dedicated to the  
187 functional exploration of human behavior (PRISME, ICM core facility, Salpêtrière Hospital, Paris,  
188 France), which allowed us to assess behavior under ecological conditions. The platform was  
189 transformed into a furnished waiting room (Figure 1A) containing specific objects that provided  
190 opportunities to interact with the environment. The PRISME platform is equipped with a six-ceiling  
191 camera system (not hidden) covering the entire waiting room. Media Recorder® software  
192 (NOLDUS Information Technology, Wageningen, the Netherlands) enables synchronous video  
193 recordings from multiple cameras over the network. During the experiment, individuals' behavior  
194 was video-recorded, and their movement acceleration was measured using a wireless body sensor

195 (Move II® triaxial accelerometer, Movisens GmbH, Karlsruhe, Germany) worn on the right hip. An  
196 eye-tracking system (SMI Eye Tracking Glasses 2 Wireless, ®SensoMotoric Instruments, Teltow,  
197 Germany) was added to the multimodal recording system, and the subjects wore eye-tracking  
198 glasses for a 7-minute period during the 45-minute experimental session. The subjects were  
199 informed at the time of initial consent that their behavior would be tracked and recorded by video  
200 cameras located in the room.

## 201 **1.2 Cohort and ethics statement**

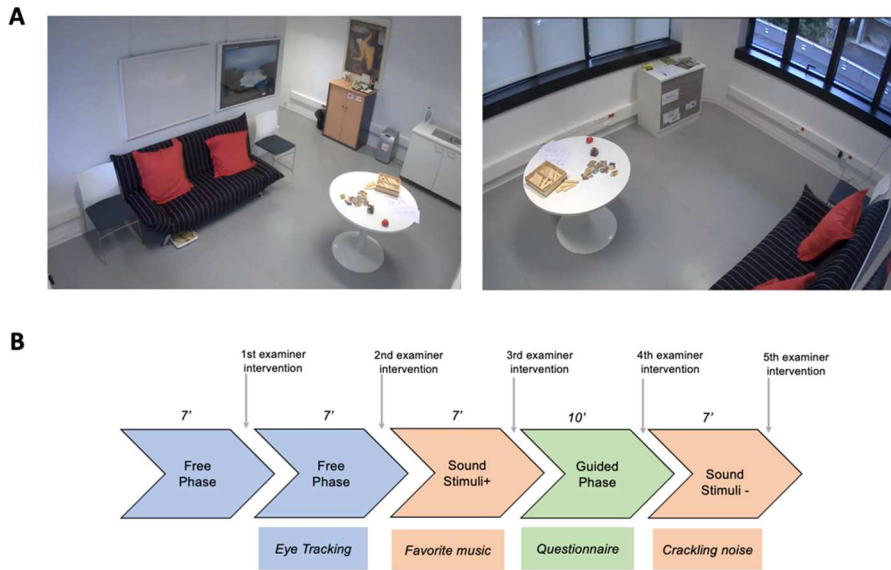
202 A cohort (ECOCAPTURE) of twenty patients with bvFTD (thirteen men and seven women)  
203 and eighteen healthy controls participated in this research. This study is part of the clinical  
204 observational study C16-87<sup>39</sup> sponsored by INSERM, the *French National Institute for Biomedical*  
205 *Research*. It was granted approval by the local Ethics Committee (*Comité de Protection des*  
206 *Personnes*, CPP) on May 17, 2017 (CPP 17-31), and was registered in a public clinical trial registry  
207 (Clinicaltrials.gov: NCT03272230). All of the study participants gave their written informed  
208 consent to participate, in line with French ethical guidelines. This study was performed in  
209 accordance with the Declaration of Helsinki. Anonymity was preserved for all participants.

## 210 **1.3 The ECOCAPTURE scenario**

211 The ECOCAPTURE paradigm of apathy assessment is driven by a 45-minute structured  
212 scenario. A general outline of the ECOCAPTURE scenario is schematically presented in Figure 1B.  
213 Outside of the waiting room, the examiner equipped the participant with an accelerometer, and then  
214 the participant was asked to wait in the room prior to the subsequent experimental tests. The subject  
215 was explicitly encouraged to make himself/herself comfortable and to enjoy the room, using the  
216 space, as well as the objects at his or her own convenience (“as if he/she was at home”). These  
217 guidelines were designed to promote the ecological validity of the behavior tracking method (i.e.,  
218 how the research context is representative of the real-life situation in which individuals’ behaviors  
219 were recorded). The scenario began with a phase called the *free phase* (FP), starting when the  
220 examiner left the room, with the subject left alone in the waiting room for a 7-minute period. Since  
221 no specific goal-directed activity was suggested by the examiner in this FP, the participants were  
222 mostly tested on their ability to self-initiate activities. This first phase (FP) was followed by several  
223 other phases, including a *guided phase* (GP) lasting 10 minutes, in which the participants were  
224 asked by the examiner to complete a questionnaire.

225 We hypothesized that the ECOCAPTURE scenario would be relevant to the study of apathy  
226 because it favors the generation of GDB under contrasting conditions and offers many different

227 opportunities to investigate the patient's behavior. We showed in a previous study that the FP is  
 228 favorable to the emergence of self-guided behavior and is conducive to exploratory behavior,  
 229 allowing us to observe how the participant behaves when discovering a novel environment to which  
 230 he or she should adapt.<sup>22</sup> This study focuses on the analysis of the self-guided behavior that  
 231 individuals develop to accomplish goals or activities during the 7-minute testing session FP. The  
 232 GP, as well as the other phases intentionally contrived by the investigators of the ECOCAPTURE  
 233 protocol (questionnaire to complete, sound stimuli), are beyond the scope of this paper.



235 **Figure 1. The ECOCAPTURE ecological setting and scenario.**

236 (A) The waiting room (PRISME, ICM) setup with different areas and specific objects that encourage a  
 237 variety of activities. The waiting room has a surface area of 24 m<sup>2</sup> and is set up with several areas that  
 238 encourage a variety of activities. The kitchen area is composed of kitchen furniture, food and drink, a cooler,  
 239 a sink and an electric kettle. The sitting area is composed of a sofa with two cushions and two chairs. Games,  
 240 such as a puzzle, Kapla, Sudoku, crosswords and a Rubik's cube, are scattered on a table in the center of the  
 241 room. In one corner of the room, a furniture (4 drawer units) contains books and magazines, as well as  
 242 candies. In the back of the room, a window with the blinds up overlooks the forecourt of the ICM building.  
 243 (B) The 45-minute structured scenario ECOCAPTURE with phase onsets (after the examiner intervention)  
 244 and phase terminations (after a fixed period). The scenario consists of five phases in the following order: a 7-  
 245 minute free phase; a 7-minute free phase with eye-tracking glasses; a 7-minute sound stimulus phase  
 246 (positive stimulus such as favorite music); a 10-minute guided phase (devoted to completing the  
 247 questionnaire); and a 7-minute sound stimulus phase (negative stimulus such as crackling noise).

248

249 **1.4 The ECOCAPTURE ethogram**

250 The ECOCAPTURE ethogram (Table 1) includes two behavioral categories: *motor patterns*  
 251 and *activity states*, focusing on the self-directed behaviors exhibited by the subjects during the free  
 252 phase. All of the behaviors included in each of these two categories are mutually exclusive (e.g.,  
 253 sitting and standing cannot occur concurrently, nor can activity and nonactivity). The *motor*  
 254 *patterns* category describes the posture, as well as the body segment movements and locomotion,  
 255 expressed by the observed individuals (e.g., sitting). The *activity states* category includes four  
 256 behaviors: 1) **nonactivity**, a state in which the subject shows no apparent activity; 2) **activity**, a  
 257 state in which the subject is engaged in an activity with sustained attention; 3) **exploration**, a state  
 258 in which the subject explores the waiting room and various objects in the room; and 4) **transition**,  
 259 focusing on the timing of transitions between states. Moreover, modifiers are used to strongly  
 260 describe and identify the nature of the activity (*activity*), as well as the exploratory behavior  
 261 (*exploration*). Each single behavior can have one and only one modifier attached. The modifiers  
 262 correspond to items present in the environment (the waiting room) with which the subject could  
 263 interact. For exploratory behavior, the modifier is indicative of the object of exploration (e.g.,  
 264 *kitchen area* or *books and magazines*). For the activity behavior, the modifier identifies a specific  
 265 activity (e.g., *food and drink* related activity or *reading*). See the full detailed ECOCAPTURE  
 266 apathy ethogram at Mendeley Data [Dataset].<sup>40</sup>

267

268 **Table 1. The ECOCAPTURE ethogram of observed behaviors during the 7-minute free phase.**

Behavior	Modifier	Description
<b>MOTOR PATTERNS (posture, movement and locomotion)</b>		
<b>Lying</b>		Subject lies down on the sofa. Subject is lying on the sofa.
<b>Sitting</b>		Subject sits on the sofa or on a chair. Subject is seated on the sofa or on a chair.
<b>Standing</b>		Subject stands. Subject is standing.
<b>Walking</b>		Subject walks and moves around the room. Subject moves at least two steps.
<b>Out of view</b>		Subject is out of sight because he or she left the waiting room (on his or her own initiative).
<b>ACTIVITY STATES</b>		
<b>Nonactivity</b>		Subject shows no apparent activity.
<b>Exploration</b>		<b>Subject explores the waiting room and objects in the room.</b>
	<i>Books and magazines</i>	Exploring books and magazines.
	<i>Furniture</i>	Exploring the furniture (4 drawer unit), opening the drawers.
	<i>Kitchen area</i>	Exploring the kitchen area (kitchen furniture, sink, cooler) and food and drink.
	<i>Games</i>	Exploring the games scattered on the table.
	<i>Outside window</i>	Standing by the window and looking outside.
	<i>Without apparent purpose</i>	Moving without apparent purpose.
	<i>Personal object</i>	Exploring or looking for a personal object (glasses, clothes).
	<i>Room</i>	Exploring miscellaneous objects in the room.
	<i>Door</i>	Going to the door.

<b>Activity</b>	<b>Subject is engaged in an activity, with sustained attention over a period of 10 seconds, for the specific reading and playing activities.</b>
<i>Reading</i>	Reading books or magazines or posters.
<i>Playing games</i>	Playing with games like the puzzle, Kapla, Sudoku, crosswords and the Rubik's Cube.
<i>Food and drink</i>	Food and drink related activities like eating, drinking and drink preparation.
<i>Tidying and cleaning</i>	Tidying the games or books and magazines. Cleaning the kitchen area.
<i>Tuning the radio</i>	Tuning the radio
<i>Space organization</i>	Carrying the tray with food and drink. Pushing or moving an object.
<i>Self-centered action</i>	Self-centered actions like taking on/off clothes, taking on/off glasses.
<i>Miscellaneous</i>	Opening or closing a window and the shutter.
<b>Transition</b>	A short-term state (a few seconds) from one state to another. Resuming a task following an interruption.
<b>Out of view</b>	Subject is out of sight because he or she left the waiting room (on his or her own initiative).

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### 1.5 The ECOCAPTURE behavior sampling protocol

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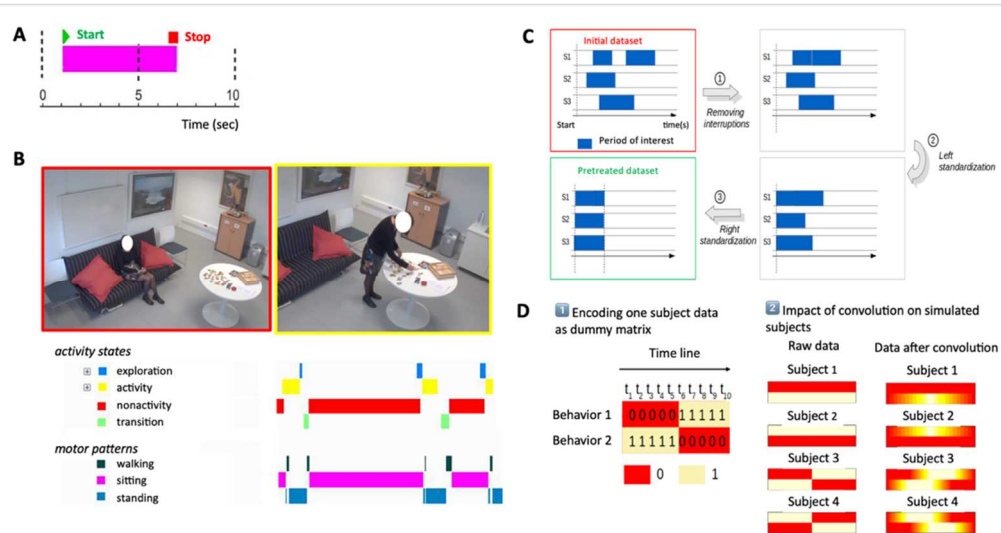
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Behavioral observations were collected through the continuous sampling method and based on the filmed material (videos), as well as the ECOCAPTURE ethogram (Table 1), by coders using a manual video annotation tool (The Observer XT®, NOLDUS Information Technology, Wageningen, the Netherlands). In this study, we focused on the behavioral data collected during a 7-minute testing session, called in this paper the *7-minute FP* period, corresponding to the free phase, to capture all of the behaviors of interest (ethogram) and their durations (states). Behavior was labeled *State*, as defined by Lehner: “the behavior an individual, or group, is engaged in; an ongoing behavior”.<sup>34</sup> Such behaviors, called *state behaviors*, have a start time and a stop time and take a period of time in such a way that allows us to calculate behavior duration (Figure 2A). The scale of measurement was an interval scale from 0 to 420, with units in seconds. For each specific behavior from the ethogram, a set of ECOCAPTURE metrics (dependent variables) were derived from the collected behavioral data to measure behavior in each participant: 1/ **behavior sequence** (a vector of structure of the type *state behavior* with the following members: start time, stop time and period of time) represents the sequence of a specific behavior during the 7-minute FP (Figure 2B); 2/ **behavior total duration** is the total duration of a behavior calculated by totaling the durations of all occurrences of the behavior, with metric values ranging from 0 to 420 sec.; and 3/ **behavior ratio** is the ratio of the total duration of a behavior to the total time of the sample session, providing the time allocated to the behavior during the 7-minute FP, interpreted as a percentage; 4/ **behavior occurrences** is the number of occurrences of a behavior during the 7-minute FP. These metrics allowed us to build **time budgets** for each participant (one per behavioral category as described in the ethogram). Time budgets are a key metric in ethology; the time budget lists the percentage of time that an individual spends performing each behavior or performing various activities.<sup>35</sup>



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295 **Figure 2. The ECOCAPTURE 7-minute testing session and the preprocessing of the collected**  
 296 **behavioral data.**

297 (A) *State behavior* has a start time and a stop time and takes a period of time (behavior duration). (B)  
 298 ECOCAPTURE - Subject ethogram data resulting from behavior continuous sampling. Example of bvFTD  
 299 patient ethogram data (The Observer XT®, NOLDUS). Sequence of each state behavior from the two  
 300 categories: *activity states* (in red: *nonactivity*; in blue: *exploration*; in yellow: *activity – playing games*; in  
 301 green: *transition*), and *motor patterns* (in dark green: *walking*; in magenta: *sitting*; in cyan: *standing*). (C)  
 302 Example of alignment of the period of interest across three virtual subjects. (D) Visualization of a dummy  
 303 matrix (1) and differences between convoluted and raw data (2).

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## 2. Participants

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A total of twenty bvFTD patients (see demographical details in Table 2) were recruited through neurological consultations at two AP-HP (Paris Public Hospitals) expert clinical sites: the national reference center on FTD at the *Institut de la Mémoire et de la Maladie d'Alzheimer* (IM2A) at the Pitié-Salpêtrière Hospital and at the Lariboisière Fernand-Widal Hospital. Diagnosis was established according to the International Consensus Diagnostic Criteria.<sup>4</sup> All of the patients met the inclusion criteria, with a Mini Mental State Examination score (MMSE)<sup>41</sup> between 20 and 30 used to determine general cognitive efficiency. Eighteen healthy controls (HCs) were recruited by public announcement and were required to score 27 out of 30 on the MMSE. HC subjects were matched to patients for age, gender and education level. Exclusion criteria for all of the participants included current or prior history of neurological disease other than bvFTD, psychiatric disease, and drug abuse.

318 The participants in the ECOCAPTURE cohort underwent the ECOCAPTURE paradigm and  
319 a comprehensive neuropsychological assessment.

320

## 321 **2.1 Neuropsychological assessment**

322 Traditional assessment of apathy severity was performed with the 14-item Starkstein Apathy  
323 Scale (SAS)<sup>11</sup>, completed by the participants (SAS self-report questionnaire). The Frontal  
324 Assessment Battery (FAB)<sup>42</sup> was used to assess cognitive function, especially frontal and executive  
325 functions. The Mattis Dementia Rating Scale (MATTIS, DRS)<sup>43</sup>, a widely used dementia screening  
326 instrument, exploring attention, initiation, perseveration, construction, conceptualization, and  
327 memory, was used to assess the individual's overall level of cognitive functioning. We used the  
328 Hospital Anxiety and Depression Scale self-administered questionnaire (HADS)<sup>44</sup> to screen for  
329 depressive symptoms and/or anxiety. The Hayling Sentence Completion Test (HSCT) examined the  
330 differing components of initiation and cognitive inhibition.<sup>45</sup> Participants were asked to complete  
331 sentences using the appropriate word (automatic condition, part A), and sentences using a  
332 completely unconnected word (inhibition condition, part B), as quickly as possible. The Hayling  
333 error score (HAYL\_ERR, total error in HSCT part B) was the outcome measure of cognitive  
334 disinhibition. Additionally, we evaluated the changes in eating behavior and its disorders using the  
335 Eating Behavior Inventory (EBI)<sup>46</sup> investigating four domains of eating behaviors: eating habits,  
336 food preference, table manners, and swallowing problems.

337

## 338 **2.2 Behavioral disinhibition assessment**

339 In addition to cognitive disinhibition, we investigated behavioral disinhibition, using  
340 behavioral disinhibitions metrics, as defined in another part of the ECOCAPTURE protocol, and  
341 one of our previous studies.<sup>23</sup> We designed an ethogram of behaviors related to disinhibition in  
342 bvFTD, according to the definitions of symptoms by Rascovsky et al.<sup>4</sup> and to previous relevant  
343 studies in the field.<sup>47,48</sup> We proposed a list of 16 behaviors, divided in three disinhibition categories:  
344 *compulsivity* (e.g., repetitive movements), *impulsivity* (e.g., inappropriate action), and *social*  
345 *disinhibition* (e.g., familiar behavior towards investigator). See the complete ECOCAPTURE  
346 ethogram at Mendeley Data<sup>40</sup>. The number of times a behavior of interest occurs per video during  
347 the 7-minute FP sample session was counted in each individual using The Observer (NOLDUS).  
348 We summed the occurrences of behaviors within each disinhibition category to obtain the score of  
349 *impulsivity*, *compulsivity*, and *social disinhibition*. These scores were then summed together to  
350 obtain the global score of *disinhibition*.

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### 3. Statistical methods

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#### 3.1 Overall

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#### 3.2 Behaviors of interest

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#### 3.3 Comparison of participants' demographic and neuropsychological scores

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All of the statistical analyses were performed using R software (version 3.6.1, R Core Team 2019) in RStudio (version 1.2.5033). The main goal of our analyses was to assess differences between bvFTD patients and HCs and to stratify the bvFTD patients according to their behavioral kinetics extracted from video encoding. We developed a method called *ECOCAPTURE kinetics* to propose a clustering approach of individuals using their behavioral kinetics based on their ethogram behavioral data. It was essential as a prerequisite to collect the input behavioral data through behavior continuous sampling and based on an ethogram consisting of categories composed of mutually exclusive state behaviors. The proposed method *ECOCAPTURE kinetics* is quite different from those of the classical approach of sequencing behaviors, producing a kinematic diagram summarizing the likelihood of various behavioral sequences.

The behavior of 20 bvFTD patients and 18 HCs was observed, and the behavioral data were collected during a single 7 minute testing session (7-minute FP) corresponding to the *ECOCAPTURE* scenario self-guided condition. We described exhaustively how subjects spent their time during the free phase and thus determined the behaviors of interest for this study (among the full range of behaviors recorded in the *ECOCAPTURE* ethogram), to which the method *ECOCAPTURE kinetics* was applied (i.e., tracking the flow of each specific behavior and analysis of state changes). To establish **time budgets** per group (bvFTD, HC), we first measured the percentage of time that each group (bvFTD patients and HC) spent on average performing each behavior from the category *activity states* and then performing various activities (as described by the set of modifiers related to the behavior *activity* in the ethogram, called **activity budget**).

To compare the participants' demographics, we used Pearson's chi-square test for gender comparison (categorical variable) and the Mann–Whitney–Wilcoxon test for the quantitative variables (age, years of education). To compare the participants' neuropsychological scores (quantitative variables), we used the Mann–Whitney–Wilcoxon test. The Shapiro-Wilk test was used to test data normality and to indicate whether the data were parametric. The significance level



384 was set at  $p < 0.05$ . Characteristics for bvFTD and HC are presented as numbers (percentages) for  
385 categorical variables and as the mean (range) and median [interquartile range] for continuous  
386 variables, and standard deviations are noted for normally distributed variables.

387

### 388 **3.4 The statistical method ECOCAPTURE kinetics**

389 The *ECOCAPTURE kinetics* method was designed to consider the time progression of each  
390 state behavior from the *activity states* and *motor pattern* categories, observed in each subject  
391 throughout the 7-minute FP. *ECOCAPTURE kinetics* are divided into five steps detailed in the  
392 following subsections. First, the data preprocessing aimed to align the data for all subjects, and the  
393 preprocessed dataset was visualized with colored bandplots. Then, the pretreated data were encoded  
394 in so-called *Subject's behavioral matrices* (SBMs), and a metric considering temporality was  
395 chosen. This metric is based on convolution principles. Finally, the bvFTD patients were classified  
396 according to the chosen metric, and the identified subgroups of patients were described and then  
397 characterized by behavioral curves and neuropsychological features.

398

#### 399 **Data preprocessing**

400 In this study, behavioral data were collected during a period of interest (7-minute FP) that  
401 should be comparable across bvFTD patients ( $n = 20$ ). Therefore, a three-step preprocessing method  
402 was applied (Figure 2C) to standardize all of the patients' sample sessions. Most of the time,  
403 periods of interest were uninterrupted (only one start and stop for a given period, i.e., the phase  
404 onset and phase termination according to the ECOCAPTURE scenario; see Figure 1B), but  
405 interruptions could also occur (several starts and stops for the same period, when a subject left the  
406 room for a moment, on his or her own initiative). In this case, the first preprocessing step consisted  
407 of removing the interruption duration(s) to obtain uninterrupted sequences. The second  
408 preprocessing step was a left standardization, causing all of the subjects to start at the same time.  
409 Indeed, the relative starting times of the period (from the start of video recording) could vary with  
410 subjects (longer time of instructions, etc.). The final step consisted of a right standardization,  
411 causing all subjects to stop the period at the same time. In this step, the minimal stop time was  
412 chosen. Figure 2C illustrates these three preprocessing (or alignment) steps. After this  
413 preprocessing, all of the subject data were comparable.

414

#### 415 **Visualization with bandplots**

416 A bandplot is an appropriate tool for visualizing successive changes in subjects' state  
417 behaviors across the period of interest. This type of diagram typically applies to a list of exclusive

418 state behaviors belonging to the same behavioral category of the ethogram. A specific color was  
419 attributed to each behavior of the list. Then, each subject's ethogram data was represented by a  
420 horizontal band with time as the abscissa, colored according to the related behavior manifested at  
421 this specific timepoint. Two bandplots were computed through the analysis of the 7-minute FP,  
422 adjusted after preprocessing alignment steps, to visualize the preprocessed behavioral data  
423 (**behavior sequence** metric). The first was related to the value states (e.g., sitting, walking) from the  
424 *motor patterns* behavioral category and is called in this paper the *motor bandplot*; the second was  
425 related to the value states (e.g., exploration, nonactivity) from *the activity states* behavioral category  
426 and is called in this paper the *activity bandplot*.

427

### 428 **Extracting subjects' behavioral matrices (SBMs) from temporal behavior data**

429 To apply our method to the ethogram data collected during the 7-minute FP (Figure 2B), we  
430 built high-dimensional time series matrices, one time series matrix per subject, in which each row  
431 corresponds to a specific behavior from the ECOCAPTURE ethogram. Our temporal approach was  
432 based on the discretization of time, which is the decomposition of the period time into  $n$  timepoints.  
433 For example, with a discretization of 1 second, if the time period lasts  $n$  seconds, the time is  
434 decomposed into  $n$  equidistant timepoints. Given one subject, every behavior occurs or not at each  
435 timepoint. This occurrence is encoded in a binary matrix with  $p$  (number of behaviors of interest)  
436 rows and  $n$  (number of timepoints) columns containing 1 if the behavior is realized at the time point  
437 or 0 otherwise. After discretizing the time into  $n$  time points, each subject's ethogram data were  
438 stored as  $p$  binary time series of size  $n$ , producing a matrix with indices of time ( $t$ ) and behavior ( $b$ ).  
439 The value of each specific metric **behavior sequence** was encoded as a binary vector (row of the  
440 matrix) to indicate the presence or absence of the related behavior. A given timepoint ( $t$ ) and  
441 behavior ( $b$ ), at which the behavior occurred was scored as 1 in the matrix cell ( $b, t$ ), and when it  
442 did not occur was scored as 0. When the dataset is correctly pretreated, the sizes of these matrices  
443 are the same across subjects. These individual dummy matrices are called in this paper *Subject's*  
444 *behavioral matrices (SBMs)* and are composed of  $p$  binary vectors of size  $n$ . Establishing a distance  
445 between such matrices is required to allow for the classification of subjects considering temporality.

446

### 447 **Choice of a metric to compare two SBMs**

448 A first intuitive method consists of using Euclidean distance between the SBMs (individual  
449 dummy matrices). However, with this approach, the distance between two subjects results from a  
450 calculation of distance at each time point without considering potential relationships between two  
451 successive time points. Consequently, the distance between two subjects exhibiting the same

452 behaviors at different timepoints will be 0, like the distance between two subjects manifesting  
 453 different behaviors at all timepoints. This property was not relevant in the context of our study and  
 454 constituted a methodological bias since we considered that two subjects exhibiting the same  
 455 behaviors were closer than subjects manifesting different behaviors.

456 To address this issue, a convolution step was used for pretreatment of the data. Convolution  
 457 is used to consider the neighborhood in imagery in convolutional neural networks and in signal  
 458 theory. For discrete signals  $f$  and  $g$  and a given time  $n$ , its calculation equals:

$$459 \quad (f * g)(n) = \sum_{m=-\infty}^{+\infty} f(m)g(n - m)$$

460 In our case,  $f$  was the binary signal for one given behavior (which can be noted as  $f(t) =$   
 461  $1_{Behavior}(t)$ ), while we chose  $g$  as a rectangular signal of unit height and width  $2M$   $[-M, +M]$  ( $M$   
 462 being defined in the next section); thus,  $f$  and  $g$  sequences were padded with 0s (from left or right)  
 463 to be defined on  $\mathbf{Z}$ , which led to:

$$464 \quad (f * g)(n) = \sum_{m=-M}^M f(n - m) = \sum_{m=-M}^M 1_{Behavior}(n - m)$$

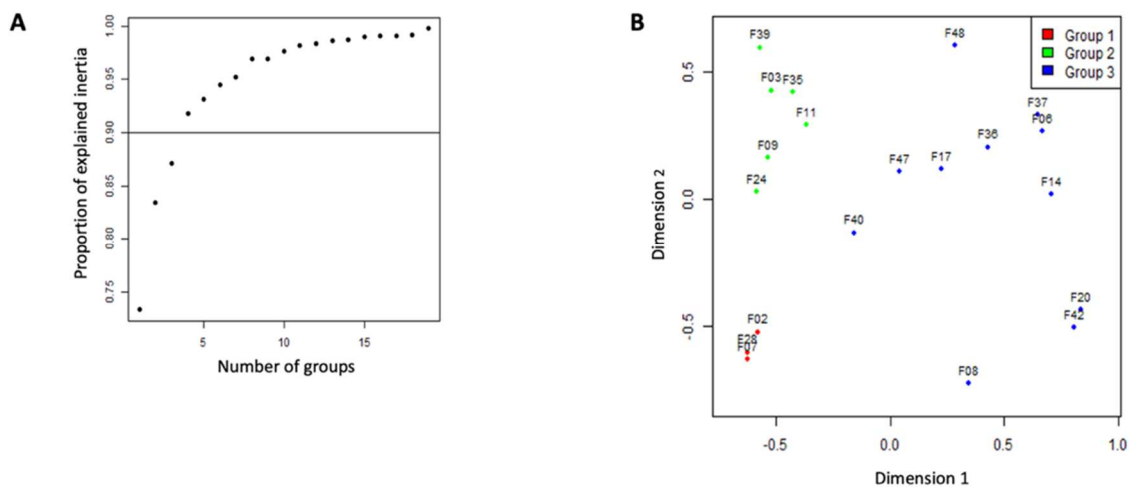
465  
 466 Consequently,  $f * g$  was the duration of behavior in the time window between  $n-M$  and  $n+M$ .  
 467 In other words, it consisted of calculating the duration of behaviors in a selected window moving  
 468 across the timeline instead of calculating global frequencies. The size of the convolution window  
 469 was chosen with  $M = 200$  for a 400-second period. With this choice, all of the signals were covered  
 470 by the convolution window. This size was also shown to maximize the discrimination between  
 471 bvFTD and HC subjects (results not shown). Each line of the SMBs was convoluted according to  
 472 this window, given a convoluted matrix. After convolution, the matrices were no longer composed  
 473 of only 0 or 1 but of a duration of behavior in the neighborhood of the function. The final step  
 474 consisted of using Euclidean distance on convoluted SMBs.

475 Figure 2D illustrates the interest of convolution: with the dataset without convolution, the  
 476 Euclidean distance between Subjects 1 and 2 (having nothing in common) was the same as that  
 477 between Subjects 3 and 4 (having the same behavior but at different timepoints). With the  
 478 convoluted dataset, the distance between Subjects 3 and 4 was lower (6.32) than the distance  
 479 between Subjects 1 and 2 (12.65) and even for a short time lower than the distance between  
 480 Subjects 1 and 3 (7.07).

481

## 482 Patient clustering and characterization of the subgroups

483 From the distance matrix, a hierarchical classification was computed with the Ward D2  
 484 method. The number of clusters was determined visually based on the scree plot criterion by  
 485 selecting the maximal number from which the gap in accumulated criteria can be seen as less  
 486 important (Figure 3A). Then, multidimensional scaling (MDS) was used to visualize on a map the  
 487 distances between the subjects with the groups assigned by the classification using the SMACOF R  
 488 package<sup>49</sup>. To characterize the different groups, behavioral curves were computed. This procedure  
 489 considers each behavior of interest separately. For each time point, the number of subjects  
 490 exhibiting this behavior was calculated. Then, these numbers were plotted against time, and a curve  
 491 was built per behavior (with potential smoothing). All behavioral curves are depicted on the same  
 492 graph with one color per behavior. This procedure was inspired by the temporal dominance of  
 493 sensations (TDS) curves in sensory analysis.<sup>50</sup> Finally, the Kruskal-Wallis test, followed by Dunn's  
 494 pairwise test with Bonferroni's correction, was used to compare the neuropsychological scores  
 495 between the groups. Boxplots were plotted to visually compare distributions in the groups of  
 496 bvFTD patients and HCs.  
 497



498 **Figure 3. Patient clustering.** (A) Explained cumulative inertia according to the number of groups. The  
 499 black line indicates a limit of 90% of explained inertia, MDS results, Stress = 0.16. (B) MDS map of the  
 500 bvFTD patients clustered in 3 groups.  
 501

502

## 503 Results

### 504 1. Intercoder reliability

505 Intercoder reliability was calculated in a subsample of eight observations. For this  
 506 subsample, two different examiners coded the videos. All calculated Cohen's kappa coefficients

507 were greater than 0.98, indicating close-to-perfect agreement between raters and therefore excellent  
508 interrater reliability.

509

## 510 **2. Cohort characteristics and neuropsychological features**

511 The bvFTD cohort (age range = 45-82 years old; mean = 65.8 years old) was composed of 7  
512 women (35%) and 13 men, with the same level of education. The demographic characteristics are  
513 shown in Table 2. The participant groups did not differ in terms of age, education, or sex  
514 distribution.

515 The neuropsychological cognitive performance, severity of behavioral changes and emotional  
516 disorders of bvFTD patients and HCs are presented in Table 2 (see Shapiro-Wilk normality test data  
517 in Supplementary Table 1).

518 A significant difference was observed for the Starkstein Apathy Scale between the two  
519 groups ( $p = 1.1e-6$ ), showing that bvFTD patients (SAS range = 7-25; mean = 15.35) were more  
520 apathetic than HCs. Higher SAS scores reflected increased endorsement of apathy in the bvFTD  
521 patients. Among the twenty bvFTD patients, fifteen were greater than or equal to the SAS  
522 pathological cutoff (14/42), while no HCs were greater than this threshold. The patients were also  
523 characterized by significant severity of depressive symptoms and anxiety as measured by the  
524 HAD.D ( $p = 3.3e-5$ ) and the HAD.A ( $p = 0.005$ ). The HADS is a screening tool using a severity  
525 cutoff for each subscale (HAD.D, HAD.A). A score of  $\geq 11/21$  is considered a clinically significant  
526 disorder, whereas a score between 8 and 10 suggests a mild disorder<sup>44</sup>. Regarding the HAD.D  
527 subscale, among the twenty bvFTD patients, five were greater than or equal to 8, including two  
528 patients greater than 10, while no HCs were greater than 3. Regarding the HAD.A subscale, among  
529 the twenty bvFTD patients, eleven were greater than or equal to 8, including four patients greater  
530 than 10, while only one HC was greater than 8. Moreover, the bvFTD patients presented a  
531 significant decrease in global cognitive efficiency, as revealed by the MMSE ( $p = 4.1e-7$ ) and  
532 MATTIS ( $p = 1.4e-7$ ), and sharp frontal syndrome, as revealed by the FAB ( $p = 2.9e-7$ ). As  
533 expected, the bvFTD patients presented more cognitive disinhibition than the HCs, exhibiting an  
534 increased rate of response error ( $p = 1e-5$ ). In the same way, bvFTD patients showed higher  
535 *compulsivity* ( $p = 0.013$ ) and *social disinhibition* ( $p = 0.018$ ) than HCs. A significant difference was  
536 also observed for the global score of *disinhibition* between the two groups ( $p = 0.006$ ). Finally,  
537 bvFTD showed changes in eating behavior compared to the HCs ( $p = 1e-6$ ).

538

539 **Table 2. Demographic characteristics, neuropsychological scores, and behavioral disinhibition**  
540 **metrics.**

541 Data are shown as N (%), mean  $\pm$  SD (range) or mean (range) and median [IQR]. *IQR* interquartile range,  
542 *SD* standard deviation, *YOE* years of education, *MMSE* Mini Mental State Examination, *FAB* Frontal  
543 Assessment Battery, *MATTIS* Mattis Dementia Rating Scale (DRS), *SAS* 14-item Starkstein Apathy Scale,  
544 *HAD* Hospital Anxiety and Depression Scale, *HAD.D* Depression, *HAD.A* Anxiety, *HAYL\_ERR* Hayling  
545 error score (number of errors in part B) in the Hayling Sentence Completion Test (HSCT), *Impulsivity*  
546 number of occurrences of behaviors within the impulsivity category, *Compulsivity* number of occurrences of  
547 behaviors within the compulsivity category, *Social disinhibition* number of occurrences of behaviors within  
548 the social disinhibition category, *Disinhibition* global score of disinhibition, *EBI* Eating Behavior Inventory.  
549 \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  for significant differences between the bvFTD and HC groups. •  $p <$   
550 0.1, for trend differences between the bvFTD and HC groups.

551

ECOCAPTURE Cohort	bvFTD	HC	Group effect	
	(n = 20)	(n = 18)	Chi <sup>2</sup> /Mann-Whitney-Wilcoxon test	
<i>Demographic information</i>				
Male sex, N%	13 (65%)	8 (44%)	$p = 0.34$	
Female sex, N%	7 (35%)	10 (56%)		
Gender (M/F)	13/7	8/10		
<b>Age (years)</b>				
mean $\pm$ SD (range)	65.8 $\pm$ 8.78 (45, 82)	62.61 $\pm$ 7.24 (46, 71)	$p = 0.17$	
median [IQR]	67 [61, 72.25]	64 [60.5, 67.5]		
<b>YOE (year)</b>				
mean $\pm$ SD (range)	13.85 $\pm$ 4.78 (7, 22)	13.78 $\pm$ 2.21 (9, 17)	$p = 0.94$	
median [IQR]	14.5 [9, 17]	14 [12, 15]		
<i>Neuropsychological data</i>			<b>p value</b>	<b>Comparison</b>
<i>Cognitive and executive functions</i>				
<b>MMSE, /30</b>				
mean $\pm$ SD (range)	24.05 $\pm$ 2.8 (20, 29)	29.39 $\pm$ 0.78 (28, 30)	$p = 4.1e-7$	bvFTD < HC ***
median [IQR]	23.5 [21.75, 26.25]	30 [29, 30]		
<b>FAB, /18</b>				
mean $\pm$ SD (range)	12.45 $\pm$ 3.41 (5, 16)	17.33 $\pm$ 0.84 (15, 18)	$p = 2.9e-7$	bvFTD < HC ***
median [IQR]	13.5 [11.5, 15]	17.5 [17, 18]		
<b>MATTIS, /144</b>				
mean $\pm$ SD (range)	119.5 $\pm$ 9.3 (104, 136)	142.17 $\pm$ 1.29 (139, 144)	$p = 1.4e-7$	bvFTD < HC ***
median [IQR]	119 [113, 125.5]	142 [141.25, 143]		
<i>Apathy</i>				
<b>SAS, /42</b>				
mean $\pm$ SD (range)	15.35 $\pm$ 4.78 (7, 25)	5.72 $\pm$ 3.08 (0, 12)	$p = 1.1e-6$	HC < bvFTD ***
median [IQR]	15.5 [13.75, 17]	6 [4, 7]		
<i>Depression, Anxiety</i>				
<b>HAD.D, /21</b>				
mean $\pm$ SD (range)	5.6 $\pm$ 3.4 (0, 12)	1.22 $\pm$ 1 (0, 3)	$p = 3.3e-5$	HC < bvFTD ***
median [IQR]	5 [3.5, 7.25]	1 [0.25, 2]		
<b>HAD.A, /21</b>				
mean $\pm$ SD (range)	7.85 $\pm$ 4.32 (1, 17)	4.22 $\pm$ 2.41 (0, 10)	$p = 0.005$	HC < bvFTD **
median [IQR]	8 [5.75, 10]	3.5 [3, 5.75]		
<i>Cognitive disinhibition</i>				
<b>HAYL_ERR</b>				
mean $\pm$ SD (range)	19.47 $\pm$ 14.42 (2, 45)	3.11 $\pm$ 2.56 (0, 8)	$p = 1e-5$	HC < bvFTD ***
median [IQR]	14 [8.5, 32]	2.5 [1, 5]		
<i>Behavioral disinhibition data</i>				
<b>Disinhibition</b>				
mean $\pm$ SD (range)	5.75 $\pm$ 8.02 (0, 31)	0.78 $\pm$ 1.56 (0, 6)	$p = 0.006$	HC < bvFTD **
median [IQR]	2.5 [0, 9]	0 [0, 1]		

<b>Impulsivity</b> mean $\pm$ SD (range) median [IQR]	2.45 $\pm$ 5.36 (0, 20) 0 [0, 1.25]	0.39 $\pm$ 1.15 (0, 4) 0 [0, 0]	$p = 0.099$	HC < bvFTD *
<b>Compulsivity</b> mean $\pm$ SD (range) median [IQR]	2.3 $\pm$ 4.03 (0, 13) 0 [0, 2.25]	0.11 $\pm$ 0.47 (0, 2) 0 [0, 0]	$p = 0.013$	HC < bvFTD *
<b>Social disinhibition</b> mean $\pm$ SD (range) median [IQR]	1 $\pm$ 1.21 (0, 5) 1 [0, 1.25]	0.28 $\pm$ 0.57 (0, 2) 0 [0, 0]	$p = 0.018$	HC < bvFTD *
<i>Eating behavior data</i>				
<b>EBI, /32</b> mean $\pm$ SD (range) median [IQR]	13.25 $\pm$ 6.03 (1, 22) 13 [10.75, 17.5]	1.33 $\pm$ 1.91 (0, 7) 0.5 [0, 2]	$p = 1e-6$	HC < bvFTD ***

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553

### 3. Behaviors of interest and time budgets

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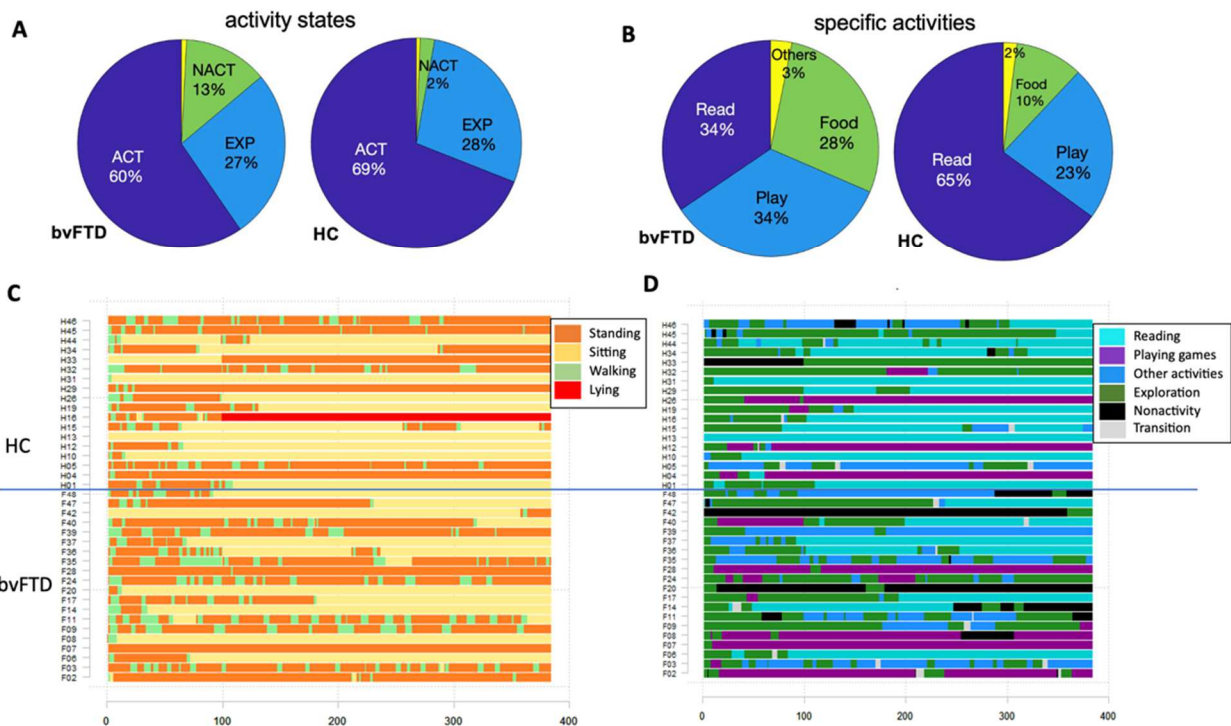
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The behaviors of interest were selected based on the time budgets of the bvFTD patients and the HCs. Figure 4A shows the **time budget** in the bvFTD and HC groups. The bvFTD patients spent more time inactive (13%) than the controls (2%). Both groups spent a large proportion of time on activities (up to 60% in bvFTD and 69% in HC). Figure 4B shows the **activity budget** in each group. In the bvFTD patients, the time spent on activities was divided between playing games (34%), reading (34%), and food and drink related activities (28%). The remaining 3% of time was spent on various activities as described in the ethogram (e.g., self-centered action). The HCs spent most of their time on similar activities as the bvFTD patients. We retained nine behaviors of interest, which are presented in Table 3.



564

565

566 **Figure 4. Subjects' behavior data are presented as time budgets and bandplots.**

567 (A) Time budgets for activity (ACT), exploration (EXP) and nonactivity (NACT) in bvFTD patients and  
 568 HCs. (B) Time budgets for reading (Read), playing games (Play), food and drink related activities (Food),  
 569 and other activities (Others) as described in the EOCAPTURE ethogram in bvFTD patients and HCs. (C)  
 570 Bandplots for motor states of the bvFTD patients (bottom) and HCs (top). (D) Bandplots for activity states of  
 571 the bvFTD patients (bottom) and HCs (top).

572

573 **Table 3.** Behaviors of interest, on which the method *ECOCAPTURE kinetics* is applied (i.e., tracking the  
 574 flow of each specific behavior and analysis of state changes).

575

Behavior	Modifier	Description
ACTIVITY STATES		
<b>1 - Nonactivity</b>		Subject shows no apparent activity.
<b>2 - Exploration</b>		Subject explores the waiting room and objects in the room.
Activity		Subject is engaged in an activity.
	<b>3 - Reading</b>	Reading books or magazines or posters.
	<b>4 - Playing games</b>	Playing with games like the puzzle, Kapla, Sudoku, crosswords and the Rubik's Cube.
	<b>5 - Other activities</b>	All other activities including the food and drink related activities.
MOTOR PATTERNS (posture, movement and locomotion)		
<b>6 - Lying</b>		Subject lies down on the sofa. Subject is lying on the sofa.
<b>7 - Sitting</b>		Subject sits on the sofa or on a chair. Subject is seated on the sofa or on a chair.
<b>8 - Standing</b>		Subject stands. Subject is standing.
<b>9 - Walking</b>		Subject walks and moves around the room. Subject moves at least two steps.

576

#### 577 **4. Bandplots**

578 Preprocessing alignment steps applied to the analysis of the 7-minute FP resulted in an  
 579 adjusted period of interest lasting approximately 400 sec. The *motor bandplot* (Figure 4C) and the  
 580 *activity bandplot* (Figure 4D) were computed through this analysis for a 400-second period. Each  
 581 bandplot is split vertically into two sub-bandplots: the 20 bottom rows correspond to the bvFTD  
 582 patients, while the 18 top rows correspond to the HCs. These visual resources allow us to visualize  
 583 the raw data and identify the sequence of behaviors of interest (Table 3) for each subject. Each row  
 584 represents the motor behavioral patterns (in the *motor bandplot*) and the activity behavioral patterns  
 585 (in the *activity bandplot*) for a particular subject. For example, the first row of the HC *motor*  
 586 *bandplot* (Figure 4C) shows orange and green band sequences throughout the 400-second period,  
 587 thus reporting that this subject exhibited these related state behaviors (standing and walking,  
 588 respectively) at these corresponding start times and for a period of time (band length).

589 Figures 4C and 4D show several interesting features of and behavioral patterns in the *motor*  
 590 and *activity bandplots*. In the *motor bandplot*, the patients show a high prevalence of walking and



591 standing sequences (orange and green bands, respectively) until the end of the 400-second period,  
592 compared to the HCs, in whom several walking and standing sequences appear narrower on the left  
593 of the timeline (i.e., the very first minutes of the analysis of the 400-second period) and are  
594 followed by a long sitting position (yellow section). In the *activity bandplot*, the temporal  
595 organization of activity reveals a specific pattern that is widely present in the HCs, in which a short  
596 exploration time (green band) is followed by a long-term activity (Reading or Playing games, or  
597 Other activities, including mainly Food and drink related activities). Compared to the HC bandplot,  
598 the bvFTD bandplot shows more large black bands (nonactivity) and a higher prevalence of blue  
599 bands (Other activities, including mainly Food and drink related activities) and overall presents a  
600 more heterogeneous behavioral pattern.

601

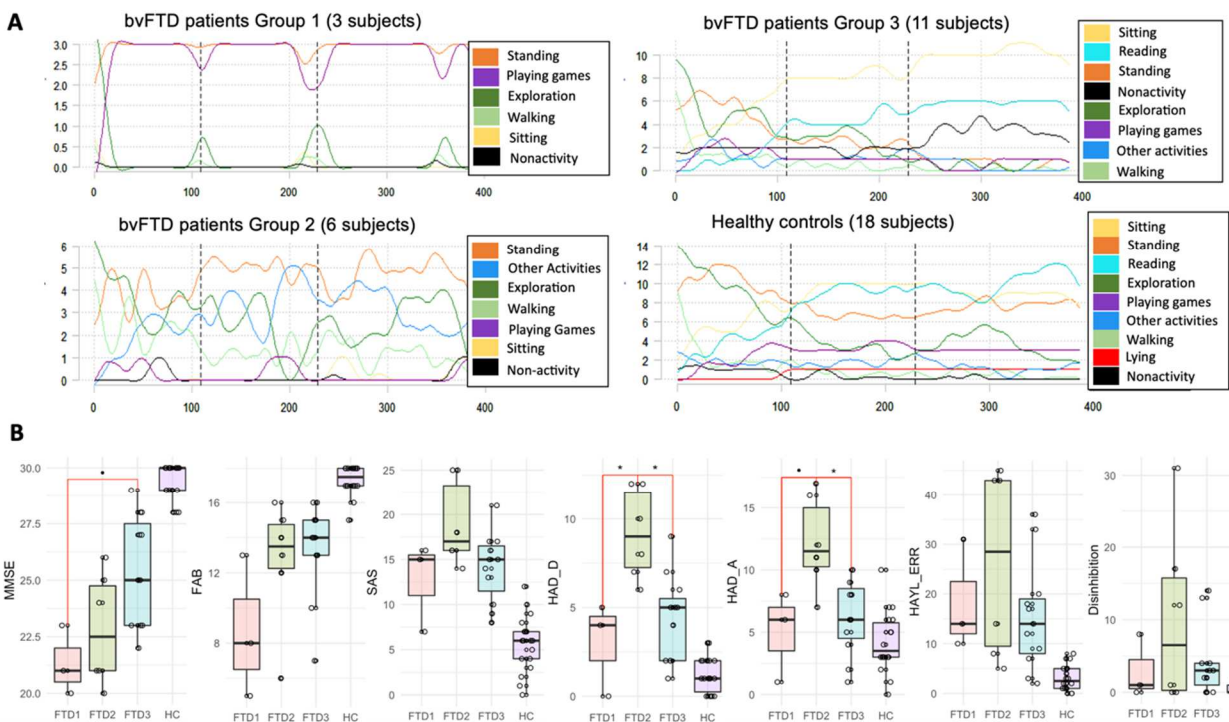
## 602 **5. Patient clustering and kinetics profiles**

603 The classification of the bvFTD patients provided the graphics of accumulated inertia  
604 presented in Figure 3A. Following a scree plot criterion, 3 groups were selected. The three  
605 subgroups of bvFTD patients were represented using MDS based on the obtained distance matrix  
606 (Figure 3B). The three subgroups contained three (Group 1), six (Group 2) and eleven (Group 3)  
607 patients. Figure 5A shows the kinetics in the three subgroups of bvFTD patients and HCs.

608 Group 1 consisted of three patients standing and playing games during the 400-second FP.  
609 Group 2 comprised six patients alternating exploration and activities, other than reading and playing  
610 games, and therefore essentially food and drink related activities, mostly standing (but sitting and  
611 walking patterns occur as well). The time diagram throughout the 400-second FP presented  
612 different types of waves. Concerning the motor pattern, the standing behavior signal had higher  
613 values and peaks, with a relatively low amplitude, since the walking signal had lower values, with a  
614 gradually decreased amplitude. Concerning the activity pattern, the activity signal and the  
615 exploration signals crossed several times. The exploration signal began with the highest value ( $n =$   
616  $6$ ), while the activity signal began with the lowest ( $n = 0$ ). Subsequently, the exploration signal  
617 decreased until  $t = 200$  sec and then increased until almost the end, while the activity signal  
618 increased from  $t = 0$  sec to  $t = 200$  sec and then decreased.

619 Group 3 consisted of eleven patients mainly sitting and reading or who were not active. The  
620 behavioral kinetics of Group 3 showed several interesting features. First, the exploration signal  
621 began with a very high value ( $n = 10$ ), but unlike Group 2, the exploration signal gradually  
622 decreased until  $t = 400$  sec, reaching very low values (1 or 0) from  $t = 240$  seconds. The reading  
623 activity signal began with the lowest value ( $n = 0$ ) and gradually increased until  $t = 250$  seconds,

624 when the waveform signal was flat ( $n = 6$ ). The two signals crossed only once, at  $t = 100$  sec.  
 625 Second, the nonactivity signal, the waveform of which was flat from the beginning, stood out as the  
 626 second highest signal ( $2 < n \leq 5$ ) after the reading signal. Third, concerning the motor pattern, the  
 627 sitting signal rapidly increased (from  $n = 1$  to 8) until  $t = 120$  sec and was maintained at a high level  
 628 (from  $n = 8$  to 11) until the end, with a flat waveform. The walking and standing signals gradually  
 629 decreased and reached low values ( $n = 0$  or 1) from  $t = 100$  sec and ( $0 < n \leq 2$ ) from  $t = 100$  sec,  
 630 respectively. Finally, the Group 3 and HC time diagrams were very close, especially with regard to  
 631 the exploration and reading signals. However, in the HCs compared to the bvFTD Group 3, the  
 632 inactivity signal had a very low level ( $0 \leq n \leq 1$ ), and the standing signal maintained a high level  
 633 during the whole 400-second period, close to that of the sitting signal.  
 634



635  
 636 **Figure 5. Behavioral kinetics and neuropsychological features of the three bvFTD groups.**  
 637 (A) Kinetics in the 3 selected groups of bvFTD patients and in the HC group. The time diagrams include the  
 638 signal throughout the 400-second FP for each behavior manifested in a particular group. (B) Distribution of  
 639 MMSE, FAB, SAS, HAD.D, HAD.A, HAYL\_ERR scores (neuropsychological data) and Disinhibition  
 640 global score (behavioral *disinhibition data*) in the selected subgroups of bvFTD patients (FTD1, FTD2,  
 641 FTD3) and HC.

642

## 643 **6. Neuropsychological profiles of the bvFTD patient subgroups**

644 We compared the selected bvFTD subgroups (called in the rest of the paper FTD1, FTD2,  
645 FTD3) with demographic, neuropsychological scores, and behavioral disinhibition metrics (Table  
646 4). Three neuropsychological variables showed significant differences (with a  $p$  value less than  
647 0.05) or trend differences (with a  $p$  value less than 0.1): MMSE (cognitive impairment), HAD.D  
648 (depression) and HAD.A (anxiety). No significant groups differences were found in overall level of  
649 cognitive functioning (MATTIS) nor in executive performance (FAB). No significant difference  
650 was observed in cognitive disinhibition (HAYL\_ERR) between the three groups of patients, nor in  
651 behavioral disinhibition (impulsivity, compulsivity, social disinhibition). There was no statistical  
652 difference in eating behavior (EBI) between the three groups of patients.

653 However, as seen previously, the whole bvFTD patients significantly differed from the HCs.  
654 Indeed, the bvFTD patients were more apathetic on SAS ( $p = 1.1e-6$ ) and characterized by severity  
655 of depressive symptoms on HAD.D ( $p = 3.3e-5$ ) and anxiety on HAD.A ( $p = 0.005$ ). They presented  
656 a global cognitive impairment on MMSE ( $p = 4.1e-7$ ) and MATTIS ( $p = 1.4e-7$ ), as well as  
657 executive deficits on FAB ( $p = 2.9e-7$ ). The bvFTD patients manifested cognitive disinhibition on  
658 HAYL\_ERR ( $p = 1e-5$ ) as well as behavioral disinhibition on ECOCAPTURE ( $p = 0.006$ ).  
659 Moreover, they showed changes in eating behavior on EBI ( $p = 1e-6$ ).

660 The FTD2 group seemed to be more apathetic (not significant) than the other groups (Figure  
661 5B), and although the statistical test was not significant, FTD2 has a higher average score (mean =  
662 19) than FTD1 (mean = 12.67) and FTD3 (mean = 14.09) on the SAS. Among the six FTD2  
663 patients, all were greater than or equal to the SAS pathological cutoff (14/42), which was not the  
664 case for FTD1 and FTD3. Moreover, FTD2 was more depressed (FTD2 > FTD1,  $p = 0.024$ ;  
665 FTD2 > FTD3,  $p = 0.018$ ) on the HAD.D and anxious on the HAD.A than the other groups  
666 (FTD2 > FTD3,  $p = 0.024$ ; FTD2 > FTD1,  $p = 0.055$ ). Regarding the HAD.D subscale, among the  
667 six FTD2 patients, four were greater than or equal to 8, including two patients greater than 10,  
668 while among the three FTD1 patients, all were less than 8, and among the eleven FTD3 patients,  
669 only one was greater than 8. Regarding the HAD.A subscale, among the six FTD2 patients, four  
670 were greater than or equal to 10, while among the three FTD1 patients, all were less than or equal to  
671 8, and among the eleven FTD3 patients, only one was greater than 8. Although no significant  
672 difference was observed in cognitive disinhibition, nor in behavioral disinhibition, between the  
673 three groups of patients, FTD2 has a higher average score (mean = 26.33) than FTD1 (mean =  
674 18.33) and FTD3 (mean = 15.07) on the HAYL\_ERR (Figure 5). In the same way, FTD2 has a  
675 higher average score (mean = 10.17) than FTD1 (mean = 3) and FTD3 (mean = 4.09) on the  
676 disinhibition global score (Figure 5), as well as on impulsivity and compulsivity categories.  
677 However, we noted that social disinhibition is almost homogeneous among all patients.

678 We also showed that FTD3 patients had higher cognitive capacity (i.e., MMSE score) than the  
 679 others (FTD3 > FTD1,  $p = 0.067$ ; FTD3 > FTD2, not significant) while being among the least  
 680 depressed (FTD3 < FTD2,  $p = 0.018$ ) and anxious patients (FTD3 < FTD2,  $p = 0.024$ ). Regarding  
 681 the MMSE, among the eleven FTD3 patients, seven were greater than or equal to 25, while all three  
 682 FTD1 patients were less than 25, and among the six FTD2 patients, only two were greater than 25.  
 683 The results were consistent for the executive functioning (FAB); among the eleven FTD3 patients,  
 684 seven were greater than or equal to 14, while all three FTD1 patients were less than 14, and among  
 685 the six FTD2 patients, only two were greater than or equal to 14. These findings underscore two  
 686 poles: a cognitive and executive pole (MMSE, FAB) and a behavioral pole (SAS, HAD.D,  
 687 HAD.A).

688

689 **Table 4. Demographic and neuropsychological characteristics in the three selected subgroups, and**  
 690 **behavioral disinhibition metrics.**

691 Data are shown as min-max (mean) or N. *YOE* Years of Education, *MMSE* Mini Mental State Examination,  
 692 *FAB* Frontal Assessment Battery, *MATTIS* Mattis Dementia Rating Scale (DRS), *SAS* the 14-item Starkstein  
 693 Apathy Scale, *HAD* Hospital Anxiety and Depression scale, *HAD.D* Depression, *HAD.A* Anxiety,  
 694 *HAYL\_ERR* Hayling error score (number of errors in part B) in the Hayling Sentence Completion Test  
 695 (HSCT). *Impulsivity* number of occurrences of behaviors within the impulsivity category, *Compulsivity*  
 696 number of occurrences of behaviors within the compulsivity category, *Social disinhibition* number of  
 697 occurrences of behaviors within the social disinhibition category, *Disinhibition* global score of disinhibition,  
 698 *EBI* Eating Behavior Inventory. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$  for significant differences between  
 699 the bvFTD groups. •  $p < 0.1$ , for trend differences between the bvFTD groups.

700

bvFTD patients	FTD1	FTD2	FTD3	Group effect	
N	3	6	11	Chi <sup>2</sup> /Kruskal-Wallis test	
<i>Demographic information</i>					
Gender (M/F)	1/2	4/2	8/3	$p = 0.45$	
Age (years)	57-70 (62.67)	58-72 (65)	45-82 (67.09)	$p = 0.31$	
Years of education	9-22 (17.67)	8-17 (12)	7-20 (13.82)	$p = 0.28$	
				<i>p</i> value	Comparison
<i>Neuropsychological data</i>					
<i>Cognitive functions</i>					
MMSE, /30	20-23 (21.33)	20-26 (22.83)	22-29 (25.45)	0.035 *	FTD3 > FTD1, $p = 0.067$ •
FAB, /18	5-13 (8.67)	6-16 (12.67)	7-16 (13.36)	0.14	
MATTIS, /144	113-127 (119.67)	104-135 (120.5)	106-136 (118.91)	0.954	
<i>Apathy</i>					
SAS, /42	7-16 (12.67)	14-25 (19)	8-21 (14.09)	0.12	
<i>Depression, Anxiety</i>					
HAD.D, /21	0-5 (3)	6-12 (9.17)	1-9 (4.36)	0.007 **	FTD2 > FTD1, $p = 0.024$ * FTD2 > FTD3, $p = 0.018$ * FTD2 > FTD3, $p = 0.024$ * FTD2 > FTD1, $p = 0.055$ •
HAD.A, /21	1-8 (5)	7-17 (12.17)	1-10 (6.27)	0.013 *	

<i>Cognitive disinhibition</i> HAYL_ERR	10-31 (18.33)	5-45 (26.33)	2-36 (15.7)	0.561	
<i>Behavioral disinhibition data</i>					
Disinhibition	0-8 (3)	0-31 (10.17)	0-14 (4.09)	0.776	
Impulsivity	0-1 (0.33)	0-20 (5.17)	0-13 (1.55)	0.508	
Compulsivity	0-7 (2.33)	0-13 (4)	0-9 (1.36)	0.703	
Social disinhibition	0-1 (0.33)	0-2 (1)	0-5 (1.18)	0.495	
<i>Eating behavior data</i>					
EBI, /32	9-22 (13.67)	2-22 (14.5)	1-21 (12.45)	0.61	

701

702

## 703 **Discussion**

704 Here, we provide a method to explore a subject's behavior under ecological settings (a  
705 waiting room) in order to contribute to the identification of apathy-like behaviors and thus the  
706 characterization of apathy.

707 in the sense that apathy can be defined as the quantitative reduction of self-generated goal-  
708 directed behaviors<sup>14</sup> and characterized in behavioral terms as “an absence of responsiveness to  
709 stimuli - internal or external - as demonstrated by a lack of self-initiated action”.<sup>12</sup> We design a  
710 framework to analyze temporal behavior data during a 7-minute period and use a temporal  
711 classification method for behavior time series data analysis. Our results show that bvFTD patients  
712 can be classified according to their behavioral kinetics. We do not pretend, at this stage of  
713 investigation, that the obtained subgroups show apathy as a multifaceted construct or that the three  
714 bvFTD subgroups match the dissociable forms of apathy or domains widely emphasized in the  
715 literature. Nevertheless, it remains relevant to further investigate each bvFTD group regarding  
716 functional markers of apathetic states. There is evidence in the literature of the multidimensional  
717 nature of apathy. Although there has been debate, most experts now consider apathy to be a  
718 syndrome and a multifaceted construct divided into separable types of apathy (emotional-  
719 affective/motivational, cognitive, autoactivation/behavioral) related to changes in a complex  
720 cerebral network of subcortical and cortical territories. However, the identification and  
721 characterization of the different components (or different forms of apathy or apathy states) remain  
722 open questions in neuroscience. Recently, Dickson & Husain (2022) argued that existing  
723 frameworks are not based on empirical evidence of clearly dissociable domains of apathy, but rather  
724 on the authors' conceptualizations from the prior literature or observations of patients with  
725 neurological conditions<sup>51</sup>, and thus the different apathy scales have been constructed, often  
726 reflecting the theoretical dimensions of the syndrome that investigators subscribe to. In their  
727 opinion, although there is evidence for behavioral and emotional domains of apathy, the contention  
728 that there might be a separate dimension of cognitive or executive apathy is far less robust.<sup>51</sup>

729 In this discussion, we attempt to further characterize each bvFTD group according to  
730 manifested apathetic behaviors while considering apathy to be secondary to different neurological  
731 and psychiatric disorders (here, bvFTD) and as such “often considered to incorporate some of the  
732 features of the related disorder or syndrome”.<sup>12</sup>

733 First, our study shows that the bvFTD patients and HCs behaved differently during the 7  
734 minutes spent in the waiting room. The motor and activity bandplots highlight differences in the  
735 way in which the bvFTD patients and HCs organize their motor and activity behavior sequences.  
736 Bandplots are an interesting opportunity to visualize all of the raw data synthetically and capture the  
737 sequential behavior patterns exhibited by both the bvFTD patients and HCs throughout the period  
738 of interest. In the HCs, the temporal organization of activity seemed to reveal a specific pattern in  
739 which a short time of exploratory behavior concurrent with walking and standing is followed by a  
740 long-term activity (in a sitting position). In the bvFTD patients, the sequence of behaviors seemed  
741 to be more erratic and less regular, globally characterized by consecutive walking and standing  
742 occurrences until the end of the period, as well as nonactivity, providing a more heterogeneous  
743 bandplot. These observed behavioral patterns are consistent with the findings from our previous  
744 study,<sup>22</sup> which reported an exploration deficit in bvFTD patients. In this previous work, we analyzed  
745 the behavioral data in 14 bvFTD patients and 14 HCs during the 7-minute FP sample session  
746 decomposed into three subsample periods. In our analysis, we were interested in measuring how  
747 long each behavior from the ethogram (Table 1) lasted in patients versus healthy controls. We  
748 showed that, during the very first minutes, when they discovered the room, the bvFTD patients  
749 manifested more inactivity and less exploratory behavior than the HC group. Therefore, in the  
750 context of facing a new environment, the HCs first explored it and then engaged in sustained  
751 activities; in contrast, the bvFTD patients were mostly characterized by inactivity and delayed  
752 exploration (they eventually explored this new place, but in a more irregular way than the HCs and  
753 several times throughout the free phase). Hence, exploratory behavior deficits under ecological  
754 conditions could be a marker of apathy in bvFTD. Moreover, it is interesting to note that  
755 exploratory behavior is of considerable interest to many scientists from different domains. First,  
756 there is evidence of links between exploration and the environment: “exploration encompasses a  
757 wide spectrum of behaviors that are concerned with gathering information about the  
758 environment”;<sup>52</sup> and exploratory behaviors in mammals have been considered reactions to novel  
759 settings.<sup>53</sup> Second, many studies have focused on exploratory behavior throughout the lifespan: 1/in  
760 humans, exploration dominates behavior for the first 9 months of life,<sup>54</sup> while 2/ there is a reduction  
761 in exploration with aging,<sup>55</sup> and 3/ aging causes a significant decline in open field exploration in  
762 rats.<sup>56</sup>

763           Second, our study confirms that bvFTD patients do not form a homogeneous group and  
764 shows that bvFTD patients manifest different behavior patterns under similar conditions. Indeed,  
765 our classification ECOCAPTURE kinetics method applied to bvFTD patients allows us to further  
766 characterize temporal patterning and, in particular, to investigate behavioral heterogeneity in the  
767 group of bvFTD patients. Interestingly, three subgroups of bvFTD patients were identified with  
768 different behavioral kinetics and neuropsychological profiles.

769           FTD1 is a very small group ( $n = 3$ ) but has the remarkable feature of constituting a group of  
770 patients who are similar to one another in respect to their kinetics profile (i.e., activity and motor  
771 behaviors). The FTD1 apathetic profile could be inferred from the following elements and the  
772 observed patients' behavior features. 1) The patients did not respond appropriately to the people  
773 (the examiner's guidelines) and external stimulation around them. Indeed, they were directly  
774 involved in an activity (playing games) without considering the environment or without taking the  
775 time to explore the room a little beforehand. It is important to note that the table on which the  
776 games were placed was located at the entrance of the room, which is one of the first areas of the  
777 room with which the subject can interact. Thus, the FTD1 patients presented a deficit in  
778 exploration. 2) The FTD1 patients exhibited self-initiated behavior (playing games); and 3) they  
779 played games during the whole free phase (the 400-second period). One can thus deduce that the  
780 FTD1 patients manifested perseverative activity with an inability to escape from it and shift among  
781 other behaviors and activities. This behavior disorder is consistent with the set of core diagnostic  
782 criteria for bvFTD, which include perseverative behavior.<sup>4</sup> 4) FTD1 patients present severe  
783 cognitive and executive impairment while they do not report themselves as anxious, depressed or  
784 apathic. This result is intuitive to suggest that cognitive impairment might be related to the patients'  
785 incapacity for rating themselves for behavioral and emotional disorders; therefore, these patients  
786 might be more apathetic than they reported. In this case, the caregivers' ratings are lacking to  
787 further characterize the severity of apathy. At the level of executive functions, the responses are  
788 those that require flexibility, selection, and so on, controlling the more automatic behaviors. When  
789 patients present severe cognitive impairment, the outcome is impaired behavior or the absence of  
790 behavior.<sup>12</sup> Here, FTD1 was characterized more by a disorder of executive cognitive functioning  
791 than by an absence or disorder of self-initiated behavior. Several studies in patients with dementia  
792 have shown a significant association between executive dysfunction and more severe apathy.<sup>57</sup>

793           FTD2 was a group of six patients alternating between activity and exploration, mostly  
794 standing (but sitting and walking patterns occurred as well). The FTD2 apathetic profile could be  
795 inferred from the following elements and observed patients' behavior features. 1) These patients  
796 manifested essentially food and drink related activities, without reading and playing very little. The

797 high prevalence of food and drink related activities is consistent with numerous studies that have  
798 shown that bvFTD patients usually have hyperphagia.<sup>58,59</sup> 2) Interestingly, exploration occurred  
799 until the end of the free phase, as if the subject could not initiate or maintain an activity (other than  
800 food and drink related activity). This form of exploratory behavior can be considered aimless  
801 wandering (nonfocused walking with little or no goal) and points to a lack of self-initiated activity  
802 in FTD2. Thus, FTD2 can be characterized by disorders related to decreased spontaneous goal-  
803 directed behavior, which could correspond either to emotional/affective apathy or to  
804 autoactivation/behavioral apathy.<sup>12,14</sup> These goal-directed behavior impairments, such as manifested  
805 in aimless exploration, are consistent with the insight provided by behavioral disinhibition measures  
806 collected during the ECOCAPTURE testing session. Indeed, FTD2 has a higher average score (no  
807 significant) than the others groups on impulsivity and compulsivity. Disinhibition disorders may  
808 limit the person's ability to focus on a goal, initiate an activity and sustain it. Interestingly, during  
809 the 7-minute FP, FTD2 exhibited the two main types of behavioral disturbances which have been  
810 distinguished in bvFTD patients: apathetic and disinhibited manifestation.<sup>3,4,60</sup> 3) Interestingly, the  
811 previous behavioral metrics were consistent with the neuropsychological data. Indeed, the FTD2  
812 patients were more apathetic (not significant) on SAS and more depressed and anxious than the  
813 other groups (significant). Apathy, depression and anxiety were explored with self-rating scales.  
814 Although self-reported data are often discussed as having methodological bias (especially  
815 concerning apathy), considering the lack of insight into bvFTD, here, it is interesting to have these  
816 three measurements targeting behavior collected in the same way. 4) The FTD2 patients presented  
817 severe cognitive disorders (MMSE, mean = 22.83) but moderate executive impairment (FAB, mean  
818 = 12.67). It is remarkable to note how much the behavioral and cognitive profile of the FTD2  
819 patients seems to match with the established criteria for bvFTD<sup>4</sup>: apathy (ECOCAPTURE, SAS),  
820 cognitive disinhibition (HAYL\_ERR), behavioral disinhibition (ECOCAPTURE) and especially  
821 impulsivity and compulsivity, global cognitive impairment (MMSE, MATTIS) and executive  
822 deficits (FAB), changes in eating behaviour (EBI), and finally a behavior dominated by food or  
823 beverage seeking behavior (ECOCAPTURE).

824 If the clinical picture of bvFTD appears clearly amongst these patients, interpretation of  
825 apathy-like behaviors remains remain less obvious. More generally, characterization of apathy  
826 remains an open question in neuroscience. Dickson & Husain (2022) highlighted evidence for  
827 behavioral and emotional blunting domains of apathy, but questioned the existence of a separate  
828 domain of cognitive or executive apathy (i.e., the inclusion of an executive dysfunction as a  
829 dimension of apathy)<sup>51</sup>: “Is cognitive apathy a reduction of goal-directed thoughts, or is it more to  
830 do with specific problems of executive ability”?



831 Furthermore, the link between apathy and other disorders is a key point, largely debated in  
832 the literature, under several neurological and/or psychiatric conditions and especially in bvFTD.<sup>61,62</sup>  
833 In their review about “the nosological position of apathy in clinical practice”, Starkstein and  
834 Leentjen<sup>63</sup> argued in favor of links between apathy and cognitive impairment, as well as between  
835 apathy and depression, and they noted that the syndrome of apathy is most frequent among  
836 individuals with neurological disorders and some degree of cognitive impairment and depression.  
837 Although apathy can occur in the absence of depression, most studies have shown that a  
838 considerable proportion of patients exhibit both apathy and depression,<sup>64</sup> and it is known that  
839 depression and apathy usually occur together in neurodegenerative diseases.<sup>65</sup> Our findings are in  
840 line with studies and confirm that it is important to continue to investigate and understand links  
841 between apathy and depression, as well as between apathy and cognitive impairment.

842 FTD3 was composed of eleven patients mainly sitting throughout the free phase. The  
843 duration of the sitting position was the main common point among all of the FTD3 patients.  
844 However, while sitting, some patients read while others were inactive; thus, the group was  
845 heterogeneous regarding the level of activity. Surprisingly, all of the FTD3 patients presented  
846 another common point, which was relatively preserved and executive cognitive functioning,  
847 regardless of the activity level. Indeed, the FTD3 patients presented only mild cognitive and  
848 executive impairments, and they had higher cognitive capacity than other patients (FTD3 > FTD1,  $p$   
849 = 0.067; FTD3 > FTD2, not significant), as well as lower cognitive disinhibition (not significant)  
850 than other patients. Moreover, the FTD3 patients rated themselves as apathetic but not depressed or  
851 anxious, and they were among the least depressed (FTD3 < FTD2,  $p$  = 0.018) and anxious patients  
852 (FTD3 < FTD2,  $p$  = 0.024). On this common neuropsychological basis, two different behaviors  
853 appeared. First, some FTD3 patients initiated and maintained reading activity for the duration of the  
854 free phase. These patients are those (among all 20 patients) whose behavior came closest to the  
855 HCs. Indeed, they exhibited the specific behavioral pattern highlighted in HCs in our previous  
856 study, in which we showed that, in the context of facing a new environment, HCs first explored it  
857 and then engaged in sustained activities [22]. FTD3 neuropsychological features confirm the  
858 proximity between FTD3 patients and HCs. Second, the other FTD3 patients sat and exhibited no  
859 activity. The key feature of apathy in these FTD3 patients without activity appeared to be relatively  
860 preserved cognitive functioning, but an absence of self-initiated activity led to a supposition of flat  
861 affect (unconcern) and could correspond to emotional/affective apathy.

862

## 863 **Limitations**

864 The present study has some limitations. First, the number of patients was limited; thus, the  
865 results remain exploratory. Further studies on a larger sample of bvFTD patients are needed. If  
866 confirmed in a larger sample of patients, this method of classification according to the behavior  
867 kinetics of individuals with apathy might identify behavioral patterns contributing to the signature  
868 symptom of apathy. Second, the behavioral data were collected from the filmed material (videos) by  
869 coders using a manual video annotation tool, and this process was very time consuming. Third, the  
870 behavioral data collection was based on an ethogram that consisted of the whole set of behaviors  
871 exhibited by individuals during a specific period under study. While an exhaustive census of all  
872 manifested behaviors might be an objective process, it is not the case when classifying them into  
873 specific behavioral categories and especially choosing the behavior units (i.e., level of behavior  
874 segmentation) and the most effective scales of analysis to measure behavior. Fourth, regarding the  
875 assessment of apathy, caregivers' ratings are lacking to better characterize the severity of apathy and  
876 manage the patients' subjectivity and anosognosia. The caregiver's version of the apathy scale  
877 should be added to the neuropsychological assessment in future studies. Fifth, regarding the  
878 assessment of depression and anxiety, we used the Hospital Anxiety and Depression Scale, which is  
879 a screening tool for use in nonpsychiatric patients to identify those with emotional distress,<sup>66</sup> but the  
880 HADS is not an interview instrument designed for the diagnosis of depression or anxiety disorders.  
881 Thus, the presence of depressive or anxiety symptoms might not be underpinned by a major  
882 depressive or anxiety disorder, and when scores  $\geq 10$ , we cannot conclude that a comorbid  
883 depression or anxiety disorder exists without a diagnostic scale; therefore, we only report the  
884 number of patients with a score greater than the threshold. To further investigate the links between  
885 apathy and depression or anxiety, an interview instrument designed for diagnosis should be added to  
886 the neuropsychological assessment in future studies. Sixth, activities of daily living (ADL) as well  
887 as instrumental activities of daily living (IADLs) measures might clarify the behavioral profile of  
888 these studied patients. The Clinical Dementia Rating scale (CDR)<sup>67</sup> should be added to the  
889 neuropsychological assessment in future studies.

890 Finally, regarding the proposed classification method, we chose a strategy based on distance  
891 analysis with convolution, but alternatives could also be considered. For example, Levenshtein's  
892 distance is used in genomics, or the Hamming distance between two strings of equal length is used  
893 in information theory. These distances (and others) are also available in the *eccptrk* R package and  
894 could also be used by the reader on his or her own data. In addition to the choice of distance, other  
895 methods of classification could be selected as parameters. Since this paper presents a proof of  
896 concept, the related R package was built as flexibly as possible and included customization of  
897 convolution parameters (such as window size), various distances and classification algorithms.

898 Another conceptual approach (not developed in the paper) could have been based on Markov chains  
899 to work on the probability of transitions between two behaviors<sup>68,69</sup> and it could be interesting to  
900 compare this approach to ours.

901

#### 902 **4. Perspectives and conclusion**

903 This paper presents a methodology to classify subjects according to their behaviors across time,  
904 considering the kinetics (and not only the state durations), and it offers free tools to visualize these  
905 behavioral kinetics (curves and bandplots). In the ECOCAPTURE study, the method applied to  
906 bvFTD patients showed the existence of three groups of patients and allowed us to investigate the  
907 key features of apathetic behaviors manifested in each of the groups, as well as the links between  
908 apathy and depression or between apathy and cognitive impairment.

909 The same type of approach could be conducted to answer other problematics in the  
910 ECOCAPTURE project or in any other research study addressing the issue of measuring behavior.  
911 For example, other phases (guided) could be analyzed instead of the free phase for bvFTD subject  
912 classification; thus, it would allow us to investigate dissociations between self-initiated behaviors  
913 and externally guided behaviors. We could further study the behavioral signature of apathy by  
914 focusing on other pathologies since apathy is secondary to different neurological and psychiatric  
915 disorders. Subjects with other neurological and/or psychiatric pathologies (e.g., depression or  
916 Alzheimer's disease) could also be classified according to their behaviors with this strategy. The  
917 choice to consider the behavior as a signal opens the door to data fusion, integrating sensor-based  
918 data, and particularly the intensity of the acceleration throughout the period studied. Over the past  
919 two decades, technological advances in sensing and mobile computing have provided researchers  
920 with new ways to collect behavioral data at a fine temporal scale both in and out of the laboratory.<sup>70</sup>  
921 Indeed, the use of a 3D accelerometer has been well established for assessing subjects' movements  
922 during activities (i.e., actigraphy). In Liu et al.,<sup>71</sup> we described the method and the preliminary  
923 results in patients with bvFTD (n=14) matched to HCs (n=14). This actigraphy study aimed to  
924 retain some metrics leading to differentiation between patients and control subjects. The data  
925 recorded were acceleration in three mutually orthogonal directions with a sample rate of 64 Hz and  
926 based on the video analysis during the free phase and the guided phase. We fixed thresholds to  
927 determine the amount of time during which the subject showed the fastest acceleration. We showed  
928 that, during the guided phase, acceleration in the bvFTD patients was significantly lower than that  
929 in the HCs. Furthermore, any other problem of classification according to behavior recorded across  
930 time could be conducted with this approach. The approach could easily be adapted to ethograms in

931 animal observation or other human behavioral experimentations. Such approaches could also be  
932 applicable to scientific fields other than behavioral studies for classifying subjects, such as sensory  
933 analysis or marketing (for evaluating the behavior of consumers across time during the viewing of  
934 an advertisement). The attributes would no longer be behaviors but sensory attributes (such as  
935 sweet, salted, etc.) or emotions (sad, happy, interested, etc.). These examples of applications are not  
936 exhaustive, and we are convinced that the extensive use of recording videos in every scientific field  
937 will lead to an increased use of these types of methods. Finally, the clinical applicability seems  
938 realistic and feasible, like a rapid clinical test or a path to early diagnosis of apathy, through a short  
939 scenario of a few minutes that would take place in a waiting room before the neurological  
940 consultation. Moreover this paradigm could be used also in clinical trials and especially to measure  
941 change in behavior after therapeutic intervention. Cognitive impairments and behavioral disorders  
942 (such as apathy, disinhibition, anxiety, stress, etc.) may be treated with pharmacological  
943 interventions as well as a variety of non-pharmacological interventions (NPI). Systematic and  
944 literature reviews have identified evidence-based nonpharmacological practices (multisensory  
945 stimulation, receptive music therapy, cognitive stimulation) to address these disorders. However, It  
946 is still not known what mechanisms are being targeted, but this is necessary to tailor these  
947 interventions accordingly and individually to increase the effectiveness of these treatments. Apathy  
948 is often targeted with NPI. This paradigm could be used to measure changes in behavior after NPI.  
949 What is relevant to determine is whether and to what extent the therapeutical intervention is  
950 efficient to reduce apathy and reinforce goal-directed behaviors. Since, complex behaviors and their  
951 disorders (e.g., distinction between cognitive and behavioral apathy) are extremely difficult to  
952 capture through questionnaires, the most robust way to assess and characterize behaviors (e.g.,  
953 apathetic-like behaviors) might be through the integration of three tools and approaches: 1) an  
954 ethological approach in natural settings and/or lab settings for observation and characterization of  
955 behaviors based on detailed ethograms, 2) passive behavioral sensing to collect sensor-based  
956 physiological data (e.g., heart rate, skin conductance, acceleration) using wearable sensors, 3)  
957 interview and neuropsychological assessment to collect active and subjective data through scales  
958 and questionnaire in patients as well as their caregivers (e.g., patient's apathy level, dyadic  
959 interaction) .

960

## 961 **Acknowledgments**

962 Part of this work was performed in the PRISME core facility of ICM. We gratefully  
963 acknowledge the scientific managers of the platform -- Mathias PESSIGLIONE and Philippe

964 FOSSATI -- as well as the valuable assistance of Pierre LEBOUCHER, Patrick KPEKOU, Pierre  
965 CANET, Gilles RAUTUREAU, and Karim NDIAYE for the setup and maintenance of the video  
966 and sensor-based data acquisition system. The authors acknowledge the support of all of the  
967 participants and their family members for contributing to this study and to the pursuit of research on  
968 apathy.

969

### 970 **Competing interests**

971 The authors report no competing interests.

972

### 973 **Data and code availability statement**

974 The preprocessed data (behavioral data coded from video), the ECOCAPTURE metrics  
975 (number of occurrences and/or total duration of each behavior during the *7-minute FP* period), and  
976 the neuropsychological data that support the findings of this study are available on Mendeley Data  
977 [dataset]<sup>72</sup>. The ECOCAPTURE ethograms (coding scheme) used for behavioral coding from video  
978 are available on Mendeley Data [dataset]<sup>40</sup>.

979 All of the functions of the proposed statistical method based on behavioral kinetics were  
980 implemented in the dedicated R package *eccptrk* (Ecocapture kinetics) and are available on GitLab  
981 [dataset]<sup>73</sup>. The R code required to reproduce the results of the paper is also available on GitLab.  
982 Therefore, the procedures can be replicated on other datasets.

983

### 984 **Study funding**

985 Part of this work was funded by grants from the ENEDIS company (ERDF), 2015-2017, and  
986 from the foundation “*Fondation pour la recherche médicale*”, FRM DEQ20150331725. The  
987 research leading to these results has received funding from the program “*Investissements d’avenir*”,  
988 ANR-10- IAIHU-06. The funders played no role in the study design, access to the data, or writing  
989 of this report.

990

### 991 **Credit Author Statement**

992 **Bénédicte Batrancourt:** Conceptualization, Methodology, Validation, Formal analysis,  
993 Investigation, Resources, Data curation, Writing - Original Draft, Visualization, Supervision,  
994 Project administration. **Caroline Peltier:** Methodology, Software, Validation, Formal analysis,  
995 Data curation, Writing - Original Draft, Visualization. **François-Xavier Lejeune:** Methodology,  
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997 **Richard Levy:** Conceptualization, Methodology, Investigation, Resources, Writing - Review &

998 Editing, Funding acquisition, Supervision, Project administration. **Frédéric Marin:** Writing -  
999 Review & Editing, Methodology. **Lars G. T. Jorgensen:** Writing - Review & Editing. **Guilhem**  
1000 **Carle:** Resources, Writing - Review & Editing. **Delphine Tanguy:** Resources, Writing - Review &  
1001 Editing. **Valérie Godefroy:** Data curation, Writing - Review & Editing. **Armelle Rametti-**  
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1007

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