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► To cite this version:

Valérie Godefroy, Anaïs Durand, Marie-Christine Simon, Bernd Weber, Joseph Kable, et al.. A structural MRI marker predicts individual differences in impulsivity and classifies patients with behavioral-variant frontotemporal dementia from matched controls. 2024. hal-04728923

HAL Id: hal-04728923

<https://hal.science/hal-04728923v1>

Preprint submitted on 9 Oct 2024

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1 A structural MRI marker predicts individual differences in impulsivity and classifies
2 patients with behavioral-variant frontotemporal dementia from matched controls

3

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29

30 **Acknowledgments**

31 This study was funded by an ANR Tremplin-ERC grant to HP, a Sorbonne Emergence Grant to HP

32 and LK, and an ERC Starting Grant to LK. Study 2 was funded by National Cancer Institute Grants

33 R01-CA-170297 to J.W.K. and C.L. and R35-CA-197461 to C.L. Study 3 was funded by grant ANR-

34 10-IAIHU-06 from the program 'Investissements d'avenir', by grant FRM DEQ20150331725 from the

35 foundation 'Fondation pour la recherche médicale', and by the ENEDIS company. FB was supported

36 by Fundação para a Ciência e Tecnologia (CEECIND/03661/2017). We thank all the participants and

37 organizers of the three studies mentioned in this paper as well as all the students who contributed to

38 help data collection.

39

40 **Data availability statement**

41 Deidentified data for the three studies are available at <https://figshare.com/s/a090ef2531a7d7b9a2e4>

42 and upon request to the first author.

43 **ABSTRACT**

44

45 Impulsivity and higher preference for sooner over later rewards (i.e., delay discounting) are
46 transdiagnostic markers of many psychiatric and neurodegenerative disorders. Yet, their
47 neurobiological basis is still debated. Here, we aimed at 1) identifying a structural MRI signature of
48 delay discounting in healthy adults, and 2) validating it in patients with behavioral variant
49 frontotemporal dementia (bvFTD)—a neurodegenerative disease characterized by high impulsivity.
50 We used a machine-learning algorithm to predict individual differences in delay discounting rates
51 based on whole-brain grey matter density maps in healthy male adults (Study 1, N=117). This resulted
52 in a cross-validated prediction-outcome correlation of $r=0.35$ ($p=0.0028$). We tested the validity of this
53 brain signature in an independent sample of 166 healthy adults (Study 2) and its clinical relevance in
54 24 bvFTD patients and 18 matched controls (Study 3). In Study 2, responses of the brain signature did
55 not correlate significantly with discounting rates, but in both Studies 1 and 2, they correlated with
56 psychometric measures of trait urgency—a measure of impulsivity. In Study 3, brain-based predictions
57 correlated with discounting rates, separated bvFTD patients from controls with 81% accuracy, and
58 were associated with the severity of disinhibition among patients. Our results suggest a new structural
59 brain pattern—the Structural Impulsivity Signature (SIS)—which predicts individual differences in
60 impulsivity from whole-brain structure, albeit with small-to-moderate effect sizes. It provides a new
61 brain target that can be tested in future studies to assess its diagnostic value in bvFTD and other
62 neurodegenerative and psychiatric conditions characterized by high impulsivity.

63

64

65 **Keywords:** brain signature; machine-learning; dementia; decision-making; delay discounting;
66 intertemporal choice; prediction

67

68 BACKGROUND

69

70 Impulsivity is the tendency to act in a rush and to seek immediate rewards without
71 consideration of potentially negative long-term consequences ¹. Trait impulsivity varies substantially
72 within the general population, with high impulsivity being a hallmark of many psychiatric and
73 neurological conditions ². Despite the many negative consequences of high impulsivity for health and
74 life in general ^{3,4}, its neurobiological correlates are still unclear, and it is unknown whether individual
75 differences in impulsivity can be reliably predicted based on structural brain features ⁵⁻⁷.
76 Neurobiological measures of impulsivity could help to understand the mechanisms and disentangle the
77 heterogeneity of symptoms related to maladaptive behavior and decision-making. Brain signatures of
78 impulsivity could also constitute new targets for diagnosis and treatment. They might aid in the
79 diagnosis and monitoring of conditions such as behavioral variant frontotemporal dementia (bvFTD)—
80 a neurodegenerative disorder characterized by frontal and temporal brain atrophy, with high impulsivity
81 and inappropriate behaviors as core symptoms ⁸. In this study, we aimed at developing a structural
82 brain signature of individual differences in impulsivity, and tested whether it could accurately classify
83 patients with bvFTD from matched healthy controls.

84 The idea that any psychological construct would depend on only one or a few isolated brain
85 regions has been more and more challenged. A new paradigm of “brain signatures” (or
86 “neuromarkers”) promoting a multivariate *brain patterns* view has therefore emerged, to complement
87 the traditional univariate brain mapping approach examining brain regions independently ⁹. Brain
88 signatures are predictive models of mental events or of individual variables (such as impulsivity) that
89 take into account distributed information across multiple brain systems ¹⁰. Brain signatures using
90 structural data are increasingly used in the field of translational neuroimaging, especially for
91 applications in patients with neurodegenerative conditions ¹¹. One of the greatest advantages of these
92 predictive models which predict behavior from brain features is that they can be tested across studies,
93 labs and populations to challenge their generalizability. We used this brain signature approach to
94 identify a network of spatially distributed structural features associated with impulsivity, as measured
95 by delay discounting. The present study applies the “component process” framework of brain
96 signatures ¹¹. Instead of predicting a given heterogenous condition such as bvFTD, we aimed at
97 identifying a predictive model of a key symptom (i.e., impulsivity), which is a common factor across

98 different diseases. This framework is also suited to the purpose of predicting a specific patient's
99 clinical profile in a perspective of personalized medicine.

100 Several arguments support the idea that delay discounting—how much people prefer smaller
101 sooner over larger later rewards—is a reliable measure of stable individual differences in a specific
102 facet of impulsivity (that is the urgency to get short-term rather than long-term reward). Individual
103 differences in delay discounting are relatively stable over time and show significant genetic heritability
104 ^{12–14}. Delay discounting moreover constitutes a potential transdiagnostic marker of conditions with high
105 impulsivity since it has been found to be altered across multiple psychiatric ¹⁵ and neurodegenerative
106 conditions ¹⁶. Recent studies have therefore started to investigate the neurobiological basis of
107 individual differences in delay discounting ^{7,14,17–23}. However, less is known about how these candidate
108 brain markers of delay discounting are expressed in psychiatric and neurological conditions
109 characterized by increased impulsivity.

110 Characterized by multiple impulsivity-related symptoms, bvFTD is a good example to
111 demonstrate the clinical potential (in particular for diagnosis) of a structural brain signature of delay
112 discounting. BvFTD is the most common clinical variant of syndromes associated with predominant
113 degeneration of the prefrontal and temporal regions as well as the basal ganglia. It is characterized by
114 significant changes in personality and behavior including disinhibition (socially inappropriate and
115 generally impulsive behaviors), as well as executive function deficits ⁸. Brain regions known to be
116 related to delay discounting such as the orbitofrontal cortex (OFC), ventromedial prefrontal cortex
117 (vmPFC) and ventral striatum ^{24–26} are often affected in bvFTD ^{27,28}. Relatedly, most studies found an
118 alteration of delay discounting in bvFTD patients compared to controls ^{16,29–32}.

119 Here, we first trained and cross-validated a structural MRI-based brain signature in a healthy
120 adult population (Study 1, N=117) using LASSO-PCR (least absolute shrinkage and selection
121 operator-principal component regression)—an established machine-learning algorithm ^{33,34} —to
122 predict individual differences in delay discounting rates from subjects' grey matter maps (N=117).
123 Brain markers of individual differences need to be tested in different and completely independent
124 samples and studies to establish their robustness and generalizability ¹⁰. Thus, in Study 2, we tested
125 the replicability of the brain signature in a second independent sample of healthy adults (N=166). In
126 Study 3, we tested the validity of the structural brain signature in a clinical population of patients with
127 behavioral variant frontotemporal dementia, who often show high impulsivity and were shown to be

128 steeper discounters (N = 42, including 24 bvFTD patients and 18 matched controls)³⁵. If a consistent
129 pattern of grey matter density across the brain can reliably predict delay discounting and more
130 generally impulsivity, then the brain-predicted discounting should be higher in bvFTD patients than in
131 controls and should be related to the level of clinically assessed impulsivity in patients. In addition to
132 testing the generalizability of the brain signature developed in Study 1, we analyzed the topographical
133 distribution of the most important structural alterations contributing to differences of brain-predicted
134 delay discounting.

135

136 **MATERIALS AND METHODS**

137

138 **Participants**

139 The research reported here complies with all relevant ethical regulations. The study protocols were
140 approved by the institutional review board of Bonn University's Medical School (Study 1), by the
141 University of Pennsylvania Institutional Review Board (Study 2), and by the French Ethics Committee
142 "Comité de Protection des Personnes Sud Méditerranée I" (Study 3).

143 *Study 1*

144 In Study 1, participants were recruited in the context of a seven-week dietary intervention study
145 (https://osf.io/rj8sw/?view_only=af9cba7f84064e61b29757f768a8d3bf) at the University of Bonn in
146 Germany. In this study, only male participants were recruited, with the following inclusion criteria: age
147 between 20 and 60 years, right-handedness, non-smoker, no excessive drug or alcohol use in the
148 past year, no psychiatric or neurological disease, body mass index (BMI) between 20 and 34, no other
149 chronic illness or medication, following a typical Western diet without dietary restrictions, and no MRI
150 exclusion criteria (e.g., large tattoos, metal in the body,). For the present purpose, we used only the
151 behavioral and structural MRI data collected during a baseline session before the dietary intervention.
152 N=117 participants were tested for the baseline session of Study 1. However, four participants were
153 excluded from the present analyses due to being outliers on grey matter density maps (three
154 participants) and due to very incoherent choices at the intertemporal choice task (one participant).
155 Thus, the data of a total of 113 participants was used for the analyses.

156 *Study 2*

157 In Study 2, participants were recruited in the context of a ten-week cognitive training study (registered
158 at clinicaltrials.gov as Clinical trial reg. no. NCT01252966) at the University of Pennsylvania, USA.
159 Individuals between 18 and 35 years of age who reported home computer and internet access were
160 recruited. Exclusion criteria were: an IQ score of <90 on Shipley Institute of Living Scale, self-reported
161 history of neurological, psychiatric, or addictive disorders (excluding nicotine), positive breath alcohol
162 reading (>0.01), color blindness, left-handedness, and claustrophobia. Here, we focused on behavioral
163 and structural MRI data collected during the baseline session before the cognitive training. In Study 2,
164 N=166 participants (mean age=24.5, 59% male) were included in the baseline session and all were
165 included in our data analyses.

166 *Study 3*

167 For Study 3, participants were recruited in the context of a clinical study at the Paris Brain Institute,
168 France (clinicaltrials.gov: NCT03272230). This study was designed to investigate the behavioral
169 correlates and neural bases of neuropsychiatric symptoms associated with behavioral variant
170 frontotemporal dementia (bvFTD). BvFTD patients were recruited in two tertiary referral centers, at the
171 Pitié-Salpêtrière Hospital and the Lariboisière Fernand-Widal Hospital, in Paris. Patients were
172 diagnosed according to the International Consensus Diagnostic Criteria⁸. To be included, bvFTD
173 patients had to present a Mini-Mental State Evaluation (MMSE) score of at least 20. Healthy controls
174 (HC) were recruited by an online announcement. Inclusion criteria included a MMSE score of at least
175 27 and matching the demographic characteristics of the bvFTD group. In total, 24 bvFTD patients
176 (mean age=66.6, 66.6% male) and 18 controls matched to patients for age and sex (mean age=62.6,
177 44.4% male) were recruited in this clinical study (see Supplementary table 1). Data of all participants
178 were used for our analyses.

179

180 **Intertemporal choice tasks**

181 *Study 1*

182 During the intertemporal choice (ITC) task performed in an MRI scanner, participants in Study 1 were
183 presented with 108 trials offering a choice between a smaller sooner (SS) reward option and a larger
184 later (LL) reward option¹⁴. Participants were informed that one of their choices could be paid out at the
185 end of the experiment, which made their choices non-hypothetical and incentive-compatible. The two
186 options were displayed on the left or right of the screen (position randomized) for 4 seconds.
187 Participants used their left or right index finger to press the response key corresponding to their choice
188 (left index for left option or right index for right option). The option chosen by the participant was then
189 highlighted by a yellow frame which remained on the screen until the end of the 4 second trial. Trials
190 were presented in randomized order (see Koban et al., 2023 for further details on the trial structure).

191 *Study 2*

192 During the ITC performed in an MRI scanner, participants had to make 120 choices between the same
193 smaller immediate reward (\$20 today) and a varying larger reward available after a longer delay (e.g.,
194 \$40 in a month)³⁶. Participants were informed that one of their choices could be paid out at the end of
195 the experiment, which made their choices non-hypothetical and incentive-compatible. Each trial

196 started with the presentation of the amount and delay of the larger later option. Once subjects had
197 made their choice, a checkmark on the screen indicated if the larger later option was chosen and a “X”
198 indicated that the immediate option was chosen for 1 s. Subjects had 4 s to make their choice.

199 *Study 3*

200 In Study 3, participants performed two ITC tasks on a computer screen, one using monetary rewards
201 (from 8 to 35 euros) and one using food rewards (from 8 to 35 chocolates) in randomized order³⁵. In
202 this study, using these two tasks allowed us to test the validity of our brain signature for the prediction
203 of discounting of several types of reward, and thus to investigate generalizability across reward
204 domains. Each of these tasks included 32 choices between SS and LL options. Participants were
205 instructed that one of their 32 choices could be randomly selected and the option that they had chosen
206 would be given to them. Thus, like in Study 1 and 2, participants’ choices were non-hypothetical and
207 incentive-compatible. For each trial, participants could indicate their choice by pressing either a blue
208 key on the keyboard with their right-hand index to select the option on the left or a yellow key with their
209 right-hand middle finger to select the option on the right. Once the choice had been made, a message
210 on the screen indicated which option had been chosen. Trials were presented in randomized order.

211

212 **Other measures of impulsivity traits and symptoms**

213 *Study 1*

214 In Study 1, along with choice data collected from the ITC task, we used self-report data from the
215 Impulsive Behavior Short Scale–8 (I-8), which measures the psychological construct of trait impulsivity
216 according to the Urgency, lack of Premeditation, lack of Perseverance, and Sensation seeking (UPPS)
217 model with four subscales comprising two items each³⁷. We predicted that the trait of *urgency*—
218 *defined as the tendency to act rashly in an emotional context* (e.g., “I sometimes do things to cheer
219 myself up that I later regret”)— would be closest to brain-predicted delay discounting, as both urgency
220 and delay discounting are supposed to measure a tendency to prefer most immediate rewards at the
221 expense of potential long-term gains.

222 *Study 2*

223 In Study 2, we used data from the UPPS-P Impulsive Behavior Scale, which measures trait impulsivity
224 according to the UPPS model with five subscales: positive urgency, negative urgency, lack of
225 premeditation, lack of perseverance, and sensation seeking³⁸. Paralleling Study 1, we predicted that

226 urgency would be the most closely related to brain-based predictions. We used the average of the
227 subscales of positive urgency (rash actions taken in response to positive emotional states) and
228 negative urgency (rash actions taken in response to negative emotional states) to test this hypothesis.

229 *Study 3*

230 This clinical study did not include a trait measure of impulsivity such as the UPPS scale. However,
231 clinical measures of core symptoms of bvFTD were available, in particular for two symptoms closely
232 related to impulsivity: inhibition deficit and dysexecutive syndrome (i.e., dysfunction in executive
233 functions). In another recent investigation of the same sample, we found that these two bvFTD
234 symptoms are related to higher discounting rates of both money and food ³⁵. We further used the
235 Hayling Sentence Completion Test (HSCT) ³⁹ considered as an objective measure of inhibition deficit,
236 and the Frontal Assessment Battery (FAB) ⁴⁰ as a measure of executive functions (lower scores
237 indicating worse executive functions). In the HSCT, participants are asked to complete 15 sentences
238 using the appropriate word, as fast as possible (automatic condition, part A), and 15 sentences using a
239 completely unrelated word (inhibition condition, part B). We used the Hayling error score (number of
240 errors in part B) as a measure of the difficulty to inhibit a prepotent response, as in Flanagan et al. ⁴¹.

241

242 **MRI data acquisition and preprocessing**

243 *Study 1*

244 Brain imaging data for Study 1 were acquired using a Siemens Trio 3T scanner. Structural images
245 were acquired using a T1 weighted MPRAGE sequence with the following parameters: TR 1660 ms;
246 TE 2.54 ms; FoV 256 mm; 208 slices; slice thickness 0.80 mm; TI 850 ms; flip angle 9°; voxel size 0.8
247 mm isomorphic; total acquisition time 6:32 min. T1 images were preprocessed for Voxel Based
248 Morphometry (VBM) analyses with SPM 12. We used the SPM module “Segment” for segmentation,
249 bias correction and rigid alignment of T1 images. These images were then used as input into the
250 DARTEL SPM module to create a customized DARTEL template and individual ‘flow fields’ for each
251 subject. DARTEL determines the nonlinear deformations for warping all grey and white matter images
252 so that they match each other. Finally, the SPM module “Normalise to MNI space” generated spatially
253 normalized grey matter images using the deformations estimated in the previous step and images
254 were spatially smoothed with a 6 mm Gaussian FWHM kernel. Among the obtained grey matter

255 images, three outliers (based on Mahalanobis distance of individual grey matter density maps with
256 Bonferroni correction) were detected and excluded from further analyses.

257 *Study 2*

258 Brain imaging data for Study 2 were acquired using a Siemens Trio 3T scanner (with a 32-channel
259 head coil). Structural images were acquired using a T1 weighted MPRAGE sequence with the
260 following parameters: TR 1630 ms; TE 3.11 ms; FOV 192x256; 160 slices; slice thickness 1 mm; TI
261 1100 ms; flip angle 15°; voxel size 0.9375 × 0.9375 × 1.000 mm; total acquisition time 4:35 min. We
262 used existing data preprocessed by Kable and colleagues³⁶. T1 images were preprocessed for VBM
263 analyses using the default preprocessing pipeline of the Computational Anatomy Toolbox (CAT12) for
264 SPM12. T1-weighted images underwent spatial adaptive non-local means (SANLM) denoising filter,
265 were bias corrected, and affine-registered, followed by standard SPM unified tissue segmentation into
266 grey matter, white matter, and cerebral spinal fluid. The grey matter volume images were spatially
267 registered to a common template using Geodesic Shooting, resampled to 1.5 mm³, and spatially
268 smoothed with an 8 mm Gaussian FWHM kernel.

269 *Study 3*

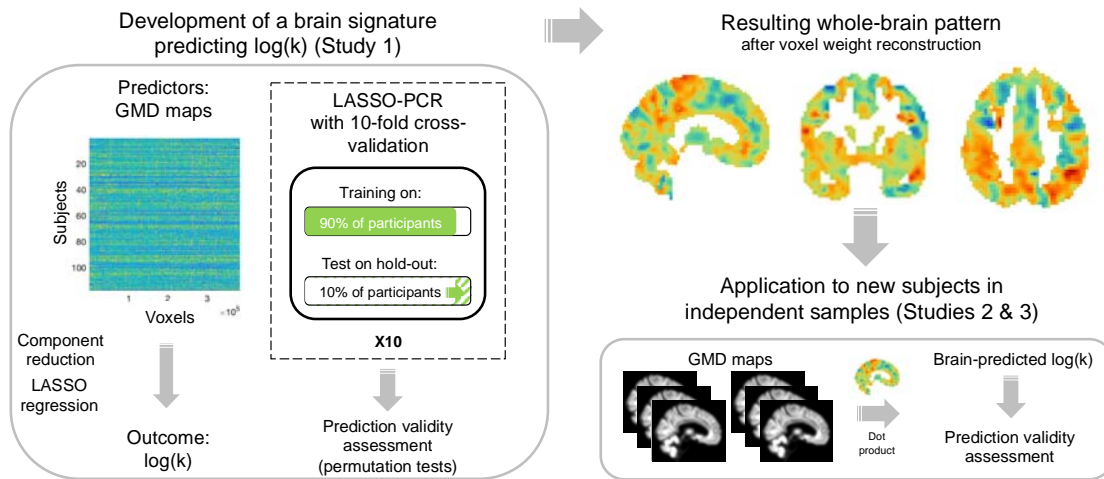
270 Brain imaging data for Study 3 were acquired using a Siemens Prisma whole-body 3T scanner (with a
271 12-channel head coil). Structural images were acquired using a T1 weighted MPRAGE sequence with
272 the following parameters: TR 2400 ms; TE 2.17 ms; FOV 224 mm; 256 slices; slice thickness 0.70
273 mm; TI 1000 ms; flip angle 8°; voxel size 0.7 mm isomorphic; total acquisition time 7:38 min. T1
274 images were preprocessed for Voxel Based Morphometry (VBM) analyses using SPM 12, following
275 the same steps as in Study 1.

276

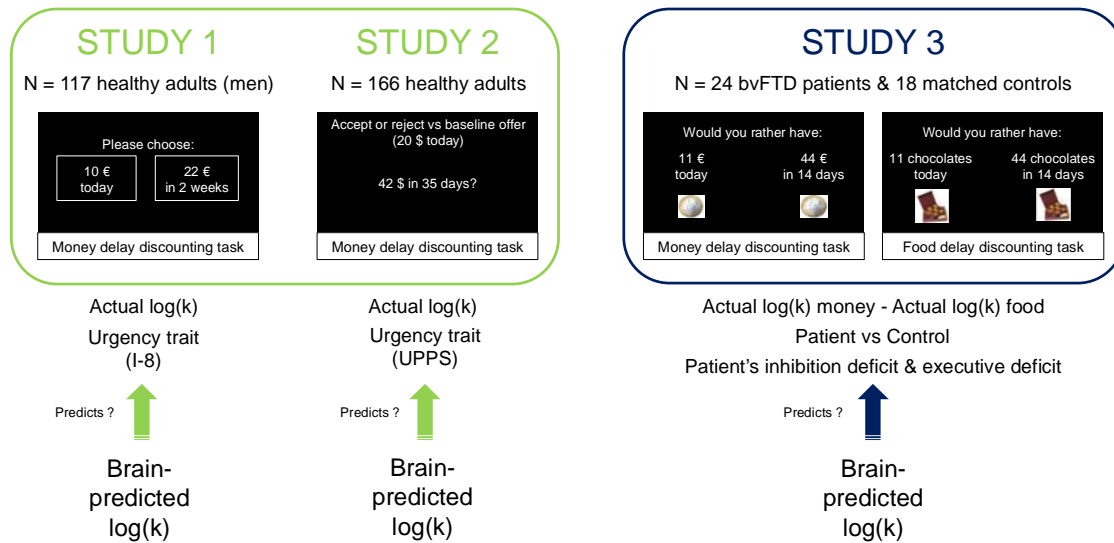
277 **Data analyses**

278 The analyses detailed in the following subsections aimed to: (1) develop and validate a structural brain
279 signature predicting delay discounting in a healthy population (Study 1); (2) test the validity of
280 predictions of this structural brain signature as measures of impulsivity in independent studies
281 involving different types of populations, including healthy (Study 2) and clinical samples (Study 3). All
282 analyses were performed using R Studio (1.2.1335) and Matlab (R2017b). The global analytic
283 approach is summarized in Figure 1A. The specific analyses conducted in each study to check the
284 validity of brain-based predictions are detailed in Figure 1B.

A. General analytic approach



B. Delay discounting paradigms and prediction validity assessment



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Figure 1. Methodological approach for the development and validation of a structural brain signature of impulsivity. A) Grey matter density (GMD) maps from healthy participants of Study 1 were used for the prediction of delay discounting ($\log(k)$) by LASSO-PCR with 10-fold cross-validation. In each fold, the classifier was trained on 90% of the data and tested on the remaining 10% hold-out data to evaluate its predictive accuracy. The predictive whole-brain pattern obtained from Study 1 was then tested in two independent samples, on the data of participants of Study 2 (healthy participants), and Study 3 (patients with neurodegenerative dementia and matched healthy control participants). The brain pattern was applied to the grey matter density maps of each study's participants to evaluate the validity of its predictions in different types of population. **B)** Several tests were performed in each of the four studies to assess the validity of the structural signature trained and cross-validated in

297 Study 1. In Study 1 (the training and cross-validation sample), permutation tests on different metrics
298 (MSE, RMSE, MAE) and in particular on the correlation between predicted and actual $\log(k)$ were
299 used to investigate the predictive accuracy of the developed brain pattern; the validity of predictions
300 was also assessed through testing their correlation with out-of-sample $\log(k)$ measured several weeks
301 later and with a self-report measure of the urgency component of impulsivity trait (subscale of
302 Impulsive Behavior Short Scale). Study 2 and 3 served as independent test samples to further validate
303 and generalize the structural signature developed in Study 1. In Study 2, we tested whether brain-
304 based predictions correlated with the actual $\log(k)$'s computed in the sample and with self-reported
305 urgency trait (mean of positive and negative urgency subscales of UPPS- Impulsive Behavior Scale).
306 In Study 3, which involved patients with behavioral variant frontotemporal dementia (bvFTD) matched
307 with healthy controls, we tested: 1) correlations between the brain pattern predictions and observed
308 delay discounting for two types of stimuli (money and food) across patients and controls; 2) the ability
309 of brain-based predictions to distinguish patients from controls; 3) correlations between measures of
310 impulsivity symptoms (inhibition and executive deficits) and brain-based predictions among patients.

311

312

313 *Computation of discount rates*

314 In all three studies, the individual discounting rate (k) was estimated by fitting logistic regressions to
315 the individual choice data, with the assumption that the subjective value (SV) of the choice options
316 followed hyperbolic discounting, as follows:

317
$$SV = \frac{A}{1 + kD}$$

318 where A is the amount of the option, D is the delay until the receipt of the reward (for immediate
319 choice, $D = 0$), and k is a discounting rate parameter that varies across subjects. Higher values of k
320 indicate greater discounting and thus higher preference for sooner rewards. In Study 1, we used
321 logistic regressions (as described in Wileyto et al., 2004) to estimate the individual parameter k from
322 the participant's answers in the ICT task at baseline and we used the $\log(k)$ values as the parameter to
323 be predicted. Individual k 's were log-transformed in all studies to obtain non-skewed distributions of
324 discounting parameters. In Study 2, we also used the $\log(k)$ values at baseline (see ³⁶). In Study 3, we
325 used the $\log(k)$ values calculated in bvFTD patients matched with controls for both monetary and food
326 rewards (see ³⁵).

327

328 *LASSO-PCR, training and cross-validation of the brain pattern predicting $\log(k)$ in Study 1*

329 We used a regression-based standard machine learning algorithm, LASSO-PCR (least absolute
330 shrinkage and selection operator-principal component regression) ³⁴, to train a classifier to predict

331 log(k) from the individual whole brain grey matter density (GMD) maps. LASSO-PCR uses principal
332 components analysis (PCA) to reduce the dimensionality of the data and LASSO regression to predict
333 the outcome (log(k)) from the extracted component scores. The components identified by the PCA
334 correspond to groups of brain regions that covary with each other in terms of grey matter density. The
335 LASSO algorithm fits a regularized regression model predicting log(k) from the identified components.
336 This algorithm iteratively shrinks the regression weights towards zero, thus selecting a subset of
337 predictors and reducing the contribution of unstable components. LASSO-PCR is suited to make
338 predictions from thousands of voxels across the whole-brain, in particular because it solves the issue
339 of multicollinearity between voxels and brain regions (see ^{43,44}). Moreover, it is possible to reconstruct
340 voxel weights across the brain (from voxel loadings on PCA components and LASSO regression
341 coefficients of components), yielding predictive brain maps that are easier to interpret than component
342 weights. To assess the accuracy of this predictive modeling from GMD maps, we used a 10-fold cross-
343 validation process. The brain classifier was trained on 90% of the data and tested on the remaining
344 10% with 10 iterations, so that each participant was used for training the model in nine folds and for
345 testing the accuracy of its prediction in the remaining fold. Ten-fold cross-validation is within the range
346 of typically recommended folds (between 5 and 10) and allowed for a large training sample size at
347 each iteration ^{45,46}. Default regularization parameters were used for all machine-learning analyses to
348 avoid overfitting of the model to the data. We used four metrics to assess the accuracy of the model
349 predictions: the mean squared error (MSE) of prediction, the root mean squared error (RMSE), the
350 mean absolute error (MAE), and the correlation between the model predictions (from the 10 hold-out
351 test samples) and observed log(k)'s (prediction-outcome correlation).

352

353 *Test of the validity of predicted log(k) in Study 1*

354 To test the reliability of the predictions, we used permutation tests assessing the statistical significance
355 of the accuracy metrics (MSE, RMSE, MAE and prediction-outcome correlation). More precisely, 5000
356 iterations of randomly permuting the log(k) values were used to generate null distributions of these
357 four metrics and thus to assess the probability of: (MSE < actual MSE), (RMSE < actual RMSE),
358 (Mean abs. error < actual Mean abs. error) and of (prediction-outcome correlation < actual prediction-
359 outcome correlation) under the null hypothesis. To further confirm the validity of out-of-sample
360 predictions of log(k), we performed correlation tests between the predicted log(k) and: (1) calculated

361 log(k) values for the ITC task performed seven weeks later (at the end of the dietary intervention); (2)
362 the urgency trait subscale of the Impulsive Behavior Short Scale–8 (I-8). Since we had directional
363 hypotheses, we used one-tailed correlation tests for all correlations between predicted and observed
364 log(k).

365

366 *Predictions of the brain pattern in an independent sample of healthy participants in Study 2*

367 To assess the predictions of the brain classifier developed in Study 1 in participants of Study 2, we
368 calculated the dot product between the predictive weight map and the grey matter density map of each
369 participant of Study 2. The dot product (computed as a linear combination of the participant's voxel
370 grey matter density multiplied by voxel weight across the brain), plus the classifier's intercept, provides
371 a pattern response and thereby a predicted value of log(k) for each participant. This allowed us to test
372 the correlations between the predicted log(k) values and: (1) the actual log(k) values computed in the
373 sample; (2) the average of positive and negative urgency measures from the UPPS-P Impulsive
374 Behavior Scale.

375

376 *Predictions of the brain pattern in patients with neurodegenerative dementia in Study 3*

377 To assess the predictions of the brain classifier developed in Study 1 in participants of Study 3, we
378 calculated again the dot product as a measure of pattern response and thereby a predicted value of
379 log(k) for each participant of Study 3. This allowed us to test: (1) the correlation between the predicted
380 log(k) and the actual log(k) values (for both monetary and food rewards) across the whole sample
381 (bvFTD patients and matched controls); (2) whether predicted log(k) values could accurately
382 discriminate between bvFTD patients and controls, using a single-interval test (thresholded for optimal
383 overall accuracy). Further, we explored whether the predicted log(k)'s were related to the severity of
384 inhibition deficit (measured by Hayling error score) and of dysexecutive syndrome (i.e., lower FAB total
385 score) among bvFTD patients.

386

387 *Bootstrapping and thresholding of the predictive brain pattern obtained in Study 1*

388 We used a bootstrapping analysis to detect the brain regions that were the most robust contributors to
389 predict log(k). Sampling with replacement from the initial sample of Study 1 participants generated
390 5,000 samples. The LASSO-PCR algorithm yielded a predictive brain pattern (voxel weights across

391 the brain) from the data (paired GMD map – log(k) outcome) in each of these 5,000 samples. For each
392 voxel weight in the whole-brain pattern, the probability of being different from 0 (either above or below
393 0) could be estimated across the 5,000 samples. Thus, two-tailed, uncorrected p-values were
394 calculated for each voxel across the whole brain and false discovery rate (FDR) correction was used
395 to correct for multiple comparisons. Bootstrapped weights were thresholded at $q=0.05$ FDR-corrected
396 across the whole weight map, as well as at $p=0.05$ uncorrected for display.

397

398 *Spatial distribution of weights in the predictive brain pattern obtained in Study 1*

399 To further characterize the spatial distribution of regions predicting log(k) and their link to different
400 functional networks, we investigated the similarity between the predictive brain pattern (resulting from
401 the LASSO-PCR procedure) and term-based meta-analytic images⁴⁷ representing functional networks
402 that have been previously hypothesized⁴⁸ to contribute to temporal discounting, namely brain areas
403 related to valuation, executive control and memory/prospection. We calculated the spatial correlation
404 coefficients (Pearson's r) between the brain pattern (map of weights) and each of the meta-analytic
405 maps (thresholded meta-analytic uniformity maps from Neurosynth) corresponding to the following list
406 of terms: "value", "reward", "emotion", "affect", "executive", "conflict", "cognitive control", "attention",
407 "planning", "imagery", "memory", "episodic memory". These spatial correlations provide descriptive
408 insight into the importance of the contribution of GMD within specific functional networks to predict
409 individual differences in delay discounting^{14,49}.

410

411 **RESULTS**

412

413 **Development and cross-validation of a structural brain signature predicting delay discounting** 414 **in healthy adults (Study 1)**

415

416 *Individual differences in impulsivity*

417 On average, participants had a fitted log(k) parameter of -5.94 (median log(k)=-5.49, corresponding to
418 $k=0.0041$). Discounting rates were characterized by substantial individual differences ($SD=2.00$), with
419 log(k) ranging from -11.92 to -2.16. These individual differences were very stable over a 7-week period
420 as reported previously¹⁴. On the I-8 subscale of urgency trait, participants' average scores varied

421 between 1 and 5 (mean=2.72; median=2.5; SD=0.84). Log(k) showed a trend for a weak positive
422 correlation with the urgency trait ($R=0.17$, $p=0.06$, 95%-CI= [-0.009, 0.35]).

423

424 *Cross-validated predictions of delay discounting - Validity of predicted log(k) in healthy participants*

425 The 10-fold cross-validation procedure revealed a significant accuracy of the brain-based prediction
426 (see Figure 2A and 2B and Supplementary figure 1): the predictions had a mean squared error of 3.45
427 (permutation test: $p=0.0026$), a root mean squared error of 1.86 (permutation test: $p=0.0026$), a mean
428 absolute error for predicted log(k) of 1.46 (permutation test: $p=0.0022$), and a cross-validated
429 prediction-outcome correlation of $R=0.35$ (permutation test: $p=0.0028$) (Figure 2C).

430 Further, supporting the reliability and conceptual validity of the brain-predicted log(k)'s, we found that
431 brain-based predictions at baseline significantly correlated with (out-of-sample) log(k)'s computed from
432 the ITC task performed seven weeks later ($R=0.34$, $p<0.001$, 95%-CI= [0.18, 1]) (Figure 2D). This
433 suggests that a relatively stable part of the between-person variability in delay discounting was
434 explained by individual differences in brain structure. Moreover, higher brain-predicted log(k) values
435 were associated with higher self-reported urgency ($R=0.20$, $p=0.037$, 95%-CI= [0.01, 0.37]) (Figure
436 2E).

437 Like the actual measures of log(k) (see ¹⁴), brain-based predictions of log(k) did not significantly
438 correlate with age ($R=-0.11$, $p=0.24$, 95%-CI= [-0.29, 0.07]), education ($R=-0.15$, $p=0.10$, 95%-CI= [-
439 0.33, 0.03]), income ($R=-0.12$, $p=0.21$, 95%-CI= [-0.30, 0.07]), BMI ($R=-0.04$, $p=0.66$, 95%-CI= [-0.22,
440 0.14]), and percentage of body fat ($R=-0.13$, $p=0.18$, 95%-CI= [-0.31, 0.06]) (see more details in
441 Supplementary figure 2).

442

443 **Performance of the Structural Impulsivity Signature in a second independent sample of healthy**
444 **participants (Study 2)**

445

446 Study 2 tests the predictions of the Structural Impulsivity Signature (SIS) in a second MRI dataset of
447 healthy participants, that has used a different protocol, scanner, different preprocessing pipeline, in a
448 socio-demographically different participant population.

449

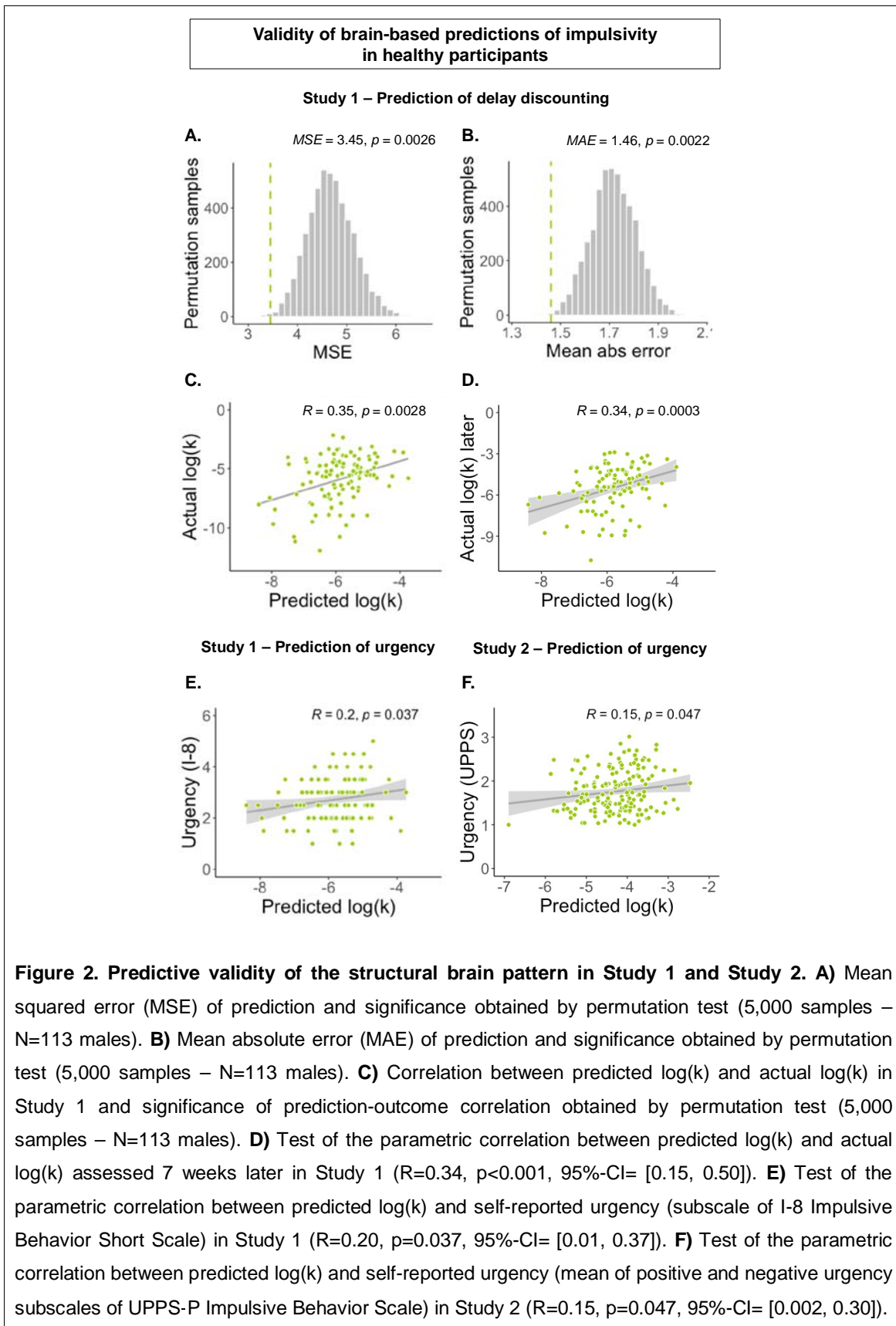
450 *Individual differences in impulsivity*

451 The mean $\log(k)$ parameter in Study 2 was -4.09 (median $\log(k)$ =-3.94, corresponding to a k of 0.019).
452 Individual differences in the discounting parameter were less variable ($SD=0.98$) as compared to
453 Study 1, with $\log(k)$ ranging from -7.08 to -2.12. Participants had average urgency trait scores (means
454 of positive and negative urgency) varying between 1.00 and 3.01 (mean=1.76; median=1.68;
455 $SD=0.48$). In Study 2, $\log(k)$ had a trend for a negative correlation with urgency ($R=-0.14$, $p=0.06$,
456 95%-CI= [-0.29, 0.008]). Therefore, in Study 2, the discounting rate does not seem to be related to
457 individual differences in impulsivity.

458

459 *Brain-based predictions of impulsivity - Validity of predicted $\log(k)$ in a second independent sample of*
460 *healthy participants*

461 For each participant in Study 2, we calculated the predicted individual $\log(k)$ as the dot-product
462 between the weight map developed in Study 1 and the individual GMD map. We then tested whether
463 predicted $\log(k)$ correlated with observed individual $\log(k)$ and with the impulsivity trait of urgency
464 (UPPS subscales). While we did not find a significant link between predicted and observed $\log(k)$ in
465 Study 2 ($R=0.06$, $p=0.21$, 95%-CI= [-0.07, 1]), predicted $\log(k)$ was positively associated with urgency
466 scales ($R=0.15$, $p=0.047$, 95%-CI= [0.002, 0.30]), see Figure 2F), as in Study 1. Thus, the results of
467 Study 2 partially validate the developed structural brain signature as a brain signature of impulsivity.



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Figure 2. Predictive validity of the structural brain pattern in Study 1 and Study 2. A) Mean squared error (MSE) of prediction and significance obtained by permutation test (5,000 samples – N=113 males). **B)** Mean absolute error (MAE) of prediction and significance obtained by permutation test (5,000 samples – N=113 males). **C)** Correlation between predicted log(k) and actual log(k) in Study 1 and significance of prediction-outcome correlation obtained by permutation test (5,000 samples – N=113 males). **D)** Test of the parametric correlation between predicted log(k) and actual log(k) assessed 7 weeks later in Study 1 ($R=0.34, p<0.001, 95\%-CI= [0.15, 0.50]$). **E)** Test of the parametric correlation between predicted log(k) and self-reported urgency (subscale of I-8 Impulsive Behavior Short Scale) in Study 1 ($R=0.20, p=0.037, 95\%-CI= [0.01, 0.37]$). **F)** Test of the parametric correlation between predicted log(k) and self-reported urgency (mean of positive and negative urgency subscales of UPPS-P Impulsive Behavior Scale) in Study 2 ($R=0.15, p=0.047, 95\%-CI= [0.002, 0.30]$).

482 **Validation of the structural brain signature in a clinical sample of bvFTD patients and matched**
483 **controls (Study 3)**

484

485 Our last analysis step aimed at further testing the generalizability of the SIS by evaluating its validity in
486 a patient population that is characterized by impulsivity. Study 3 employed a distinct protocol from
487 Studies 1 and 2 (different ITC task, different MRI scanner and parameters), and in a different, older
488 population including dementia patients with substantial structural atrophy. This further allowed us to
489 investigate the clinical relevance of the SIS (1) for classifying patients with bvFTD differently from
490 matched control participants and (2) for predicting the core symptoms of disinhibition and executive
491 deficits in patients with bvFTD⁸.

492

493 *Differences of impulsivity between bvFTD patients and healthy controls*

494 In line with the core symptoms of this disorder, bvFTD patients presented significantly higher delay
495 discounting (i.e. more impatient or impulsive choices) compared to controls, for both money rewards
496 and food rewards (see³⁵). They also showed higher inhibition deficit (Hayling-error score; $t=5.71$,
497 $p<0.001$, Cohen's $d=1.60$, 95%-CI=[0.87, 2.33]) and lower executive performances (FAB score; $t=-$
498 7.31 , $p<0.001$, Cohen's $d=-2.00$, 95%-CI=[-1.23, -2.77]) compared to controls (see Supplementary
499 table 1).

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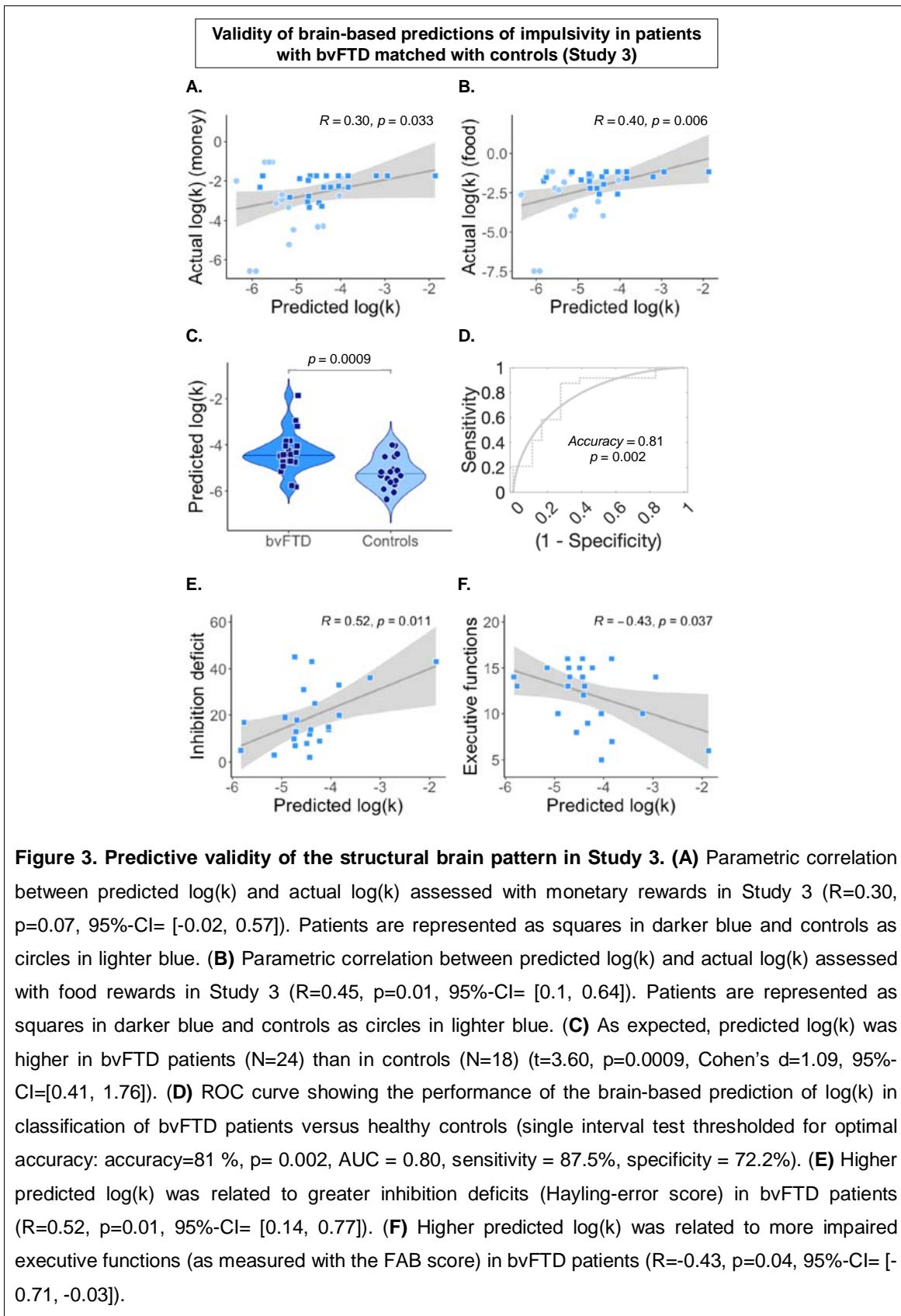
501 *Brain-based predictions of impulsivity – Validity of predicted log(k) in bvFTD patients*

502 To investigate the predictive validity of our classifier in Study 3, we first tested whether predicted
503 log(k)'s (obtained from the brain pattern applied to each participant's grey matter density map) were
504 correlated with actual log(k)'s calculated in this study across the whole sample (patients and controls).
505 This analysis showed that the predicted log(k) values were positively correlated with actual log(k)
506 values, for both monetary rewards ($R=0.30$, $p=0.03$, 95%-CI= [0.03, 1], mean absolute error of 2.08)
507 and for food rewards ($R=0.40$, $p=0.006$, 95%-CI= [0.15, 1], mean absolute error of 2.65) (see Figure
508 3.A and 3.B).

509 We next tested whether the SIS predictions could distinguish bvFTD patients from controls. As
510 expected, we found that brain-predicted log(k) was significantly higher in bvFTD patients than in
511 controls ($t=3.60$, $p= 0.0009$, Cohen's $d=1.09$, 95%-CI=[0.41, 1.76] – see Figure 3.C). Notably, brain-

512 predicted log(k) significantly predicted whether a grey matter density map was from a bvFTD patient or
513 from a control participant, with a classification accuracy of 81 % ($p= 0.002$, sensitivity = 87.5%,
514 specificity = 72.2%, - see Figure 3.D). Interestingly, the actual log(k)'s calculated for monetary and
515 food rewards in this sample revealed slightly lower predictive accuracies and especially lower
516 specificities: 73.7 % accuracy for monetary rewards ($p= 0.07$, sensitivity = 100%, specificity = 37.5%,)
517 and 76.3 % for food rewards ($p= 0.01$, sensitivity = 100%, specificity = 47.1%).

518 We next investigated the relationship between brain-predicted log(k) and clinical measures of bvFTD
519 core symptoms of disinhibition and executive deficits. Across both the patient and control groups,
520 higher predicted log(k) was associated with higher inhibition deficit (higher Hayling-error score;
521 $R=0.55$, $p=0.0002$, 95%-CI= [0.30, 0.74]) and higher executive troubles (lower FAB score; $R=-0.56$,
522 $p=0.0001$, 95%-CI= [-0.74, -0.30]). More interestingly, even within the group of bvFTD patients, higher
523 predicted log(k) was associated with higher inhibition deficit (higher Hayling-error score; $R=0.52$,
524 $p=0.01$, 95%-CI= [0.14, 0.77]) and higher executive troubles (lower FAB score; $R=-0.43$, $p=0.04$, 95%-
525 CI= [-0.71, -0.03]) (see Figure 3.E and 3.F). Further, we checked that predicted log(k) was still
526 significantly related to lack of inhibition (i.e., higher Hayling-error scores; $B=8.63$, $p=0.02$, 95%-CI=
527 [1.51, 15.7]) within bvFTD patients even after controlling for executive function deficit; this added result
528 showed that the relationship between brain-based predictions and disinhibition symptom was not only
529 due to shared variance with the severity of dysexecutive syndrome. Together, these findings show that
530 the SIS significantly and accurately classified bvFTD patients from matched controls, and that it
531 tracked the severity of key symptoms in these patients.



532

533 **Figure 3. Predictive validity of the structural brain pattern in Study 3.** (A) Parametric correlation
534 between predicted log(k) and actual log(k) assessed with monetary rewards in Study 3 ($R=0.30$,
535 $p=0.07$, 95%-CI= [-0.02, 0.57]). Patients are represented as squares in darker blue and controls as
536 circles in lighter blue. (B) Parametric correlation between predicted log(k) and actual log(k) assessed
537 with food rewards in Study 3 ($R=0.45$, $p=0.01$, 95%-CI= [0.1, 0.64]). Patients are represented as
538 squares in darker blue and controls as circles in lighter blue. (C) As expected, predicted log(k) was
539 higher in bvFTD patients ($N=24$) than in controls ($N=18$) ($t=3.60$, $p=0.0009$, Cohen's $d=1.09$, 95%-
540 CI=[0.41, 1.76]). (D) ROC curve showing the performance of the brain-based prediction of log(k) in
541 classification of bvFTD patients versus healthy controls (single interval test thresholded for optimal
542 accuracy: accuracy=81 %, $p = 0.002$, AUC = 0.80, sensitivity = 87.5%, specificity = 72.2%). (E) Higher
543 predicted log(k) was related to greater inhibition deficits (Hayling-error score) in bvFTD patients
544 ($R=0.52$, $p=0.01$, 95%-CI= [0.14, 0.77]). (F) Higher predicted log(k) was related to more impaired
545 executive functions (as measured with the FAB score) in bvFTD patients ($R=-0.43$, $p=0.04$, 95%-CI= [-
546 0.71, -0.03]).

547

548

549 **Spatial distribution of weights in the structural brain signature (Study 1)**

550

551 *Thresholded pattern of structural brain signature*

552 Bootstrapping results revealed the positive and negative weights that most strongly contributed to
553 GMD-based prediction of individual differences in delay discounting. At a threshold of $q=0.05$ FDR-
554 corrected, we found two clusters in which grey matter density positively contributed to discounting
555 differences (which means that higher grey matter density was associated with higher impatience);
556 these clusters were in the left lateral parietal cortex (supramarginal gyrus) and left lateral occipital
557 cortex (superior division). At a threshold of $p=0.001$ uncorrected, we found additional clusters
558 contributing positive weights, especially in regions of the valuation system⁵⁰ such as the right
559 orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and right ventral striatum.

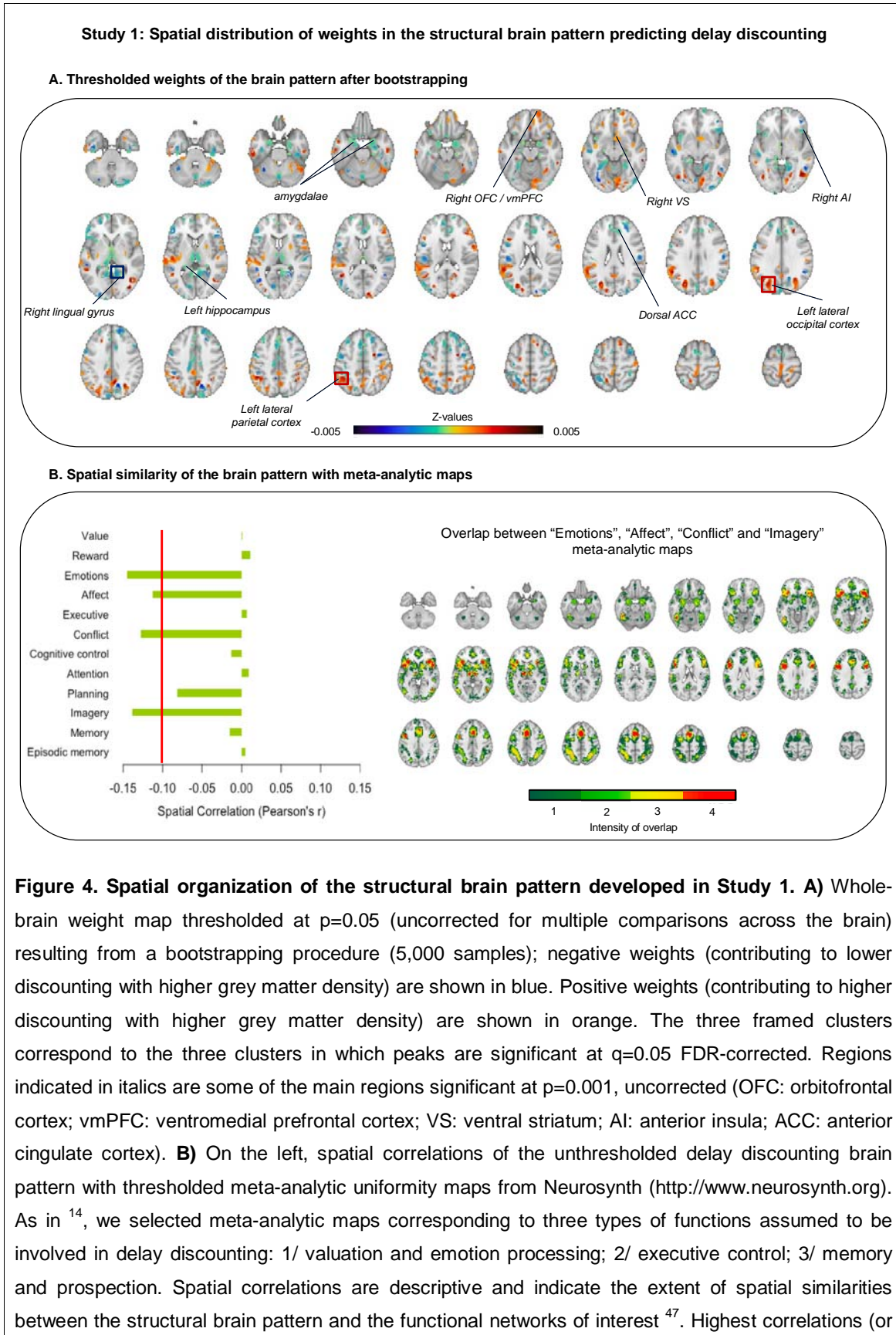
560 At $q=0.05$ FDR-corrected, there was one cluster in the posterior cingulate cortex (PCC) and adjacent
561 lingual gyrus (including retrosplenial cortex) in which grey matter density contributed negatively to
562 discounting differences (i.e., in which lower grey matter density was associated with higher
563 impatience). At a threshold of $p=0.001$ uncorrected, other important regions contributing negative
564 weights were found in the left hippocampus, the right anterior insulae (AI), dorsal anterior cingulate
565 cortex (ACC), and amygdalae. For display purposes, the bootstrapped weight map is displayed in
566 Figure 3A at a more comprehensive threshold ($p=0.05$ uncorrected, see also Supplementary table 2).

567

568 *Similarity of structural brain signature to meta-analytic maps*

569 When comparing the predictive map of $\log(k)$ with meta-analytic uniformity maps⁴⁷, we observed that
570 the highest similarities (spatial correlation r 's > 0.1 in absolute value) were with the "Emotions",
571 "Affect", "Conflict" and "Imagery" meta-analytic maps (Figure 4B). These spatial correlations were all
572 negative, indicating that greater grey matter density in areas related to emotions, affect, conflict
573 processing, and imagery contributes to predicting lower delay discounting or more 'patient' decision-
574 making (or conversely, lower grey matter density in these areas predicts higher discounting and more
575 impulsive decision-making). The "Emotions", "Affect", "Conflict" and "Imagery" meta-analytic maps
576 correspond to overlapping functional networks (see Figure 4.B). Among the most overlapping regions
577 between these four networks (in red), the AI and dorsal ACC, corresponding to robust negative
578 weights in the brain pattern, are known to be major hubs of the salience network⁵¹.

579



596 similarities) were observed with the “Emotions”, “Affect”, “Conflict”, and “Imagery” meta-analytic maps,
597 and were all negative, meaning that higher grey matter density in these functional regions is
598 associated with lower discounting. On the right, we show the spatial distribution and overlap between
599 the four meta-analytic maps found to be the most negatively correlated with the structural brain pattern
600 (from 1, corresponding to non-overlapping regions from only one map, to 4, corresponding to regions
601 of overlap between the 4 maps).

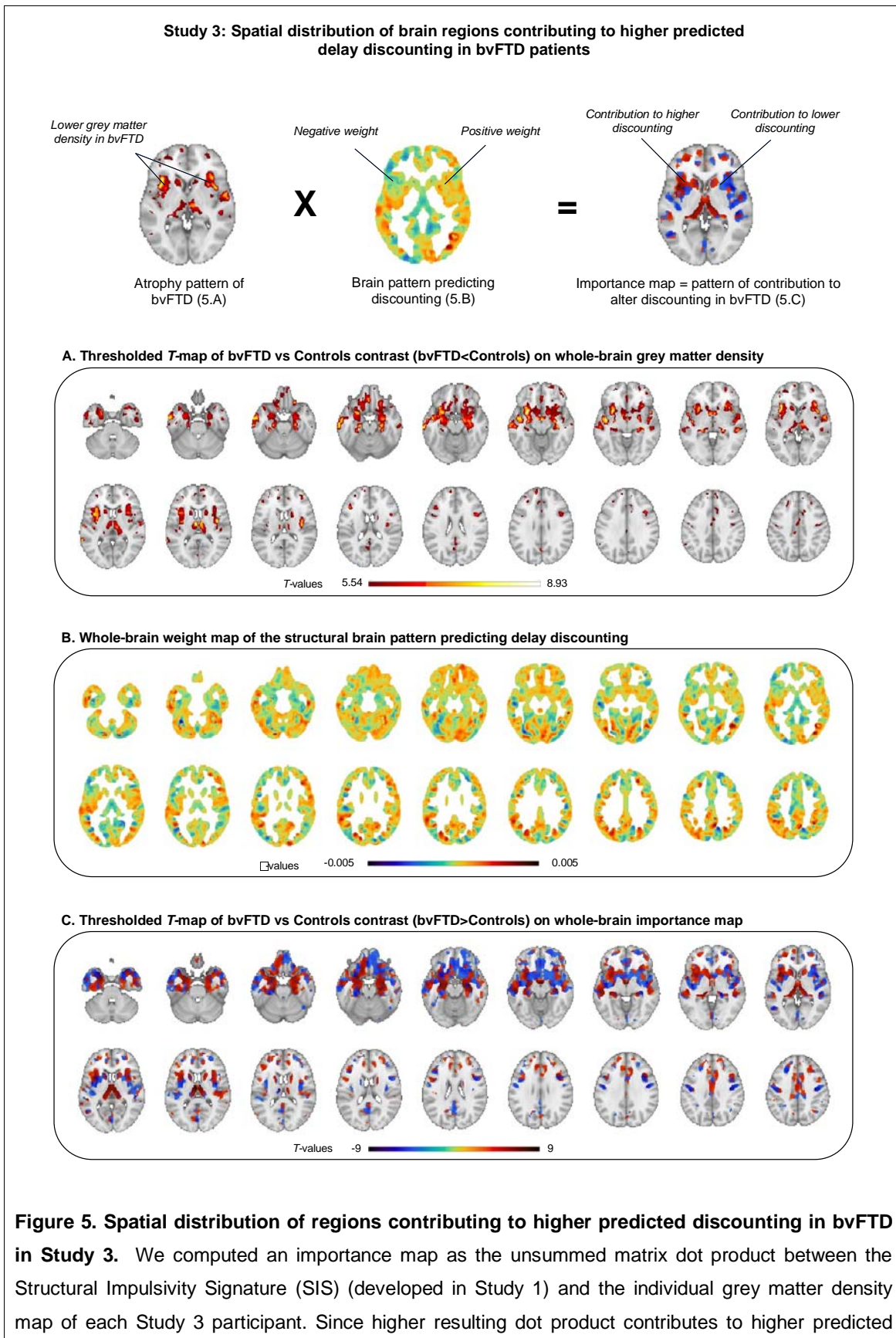
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604 **Spatial distribution of brain regions contributing to higher predicted $\log(k)$ in bvFTD (Study 3)**

605 To identify the main brain regions which contributed to differentiate bvFTD patients from controls on
606 the brain-predicted $\log(k)$, we contrasted bvFTD patients versus controls in terms of voxel-wise pattern
607 expression of the predictive map of $\log(k)$. To this end, for each bvFTD patient and each control
608 participant, we computed an ‘importance map’ as the unsummed matrix dot product between the
609 predictive structural weight map and the individual grey matter density map. Since higher resulting dot
610 product contributes to higher predicted discounting, the importance map shows which brain regions
611 contributed to increase (or decrease) predicted discounting in each individual. We performed a t-test
612 contrasting bvFTD patients and controls (bvFTD > controls) on the resulting importance maps, with a
613 family-wise error (FWE) correction applied to p-values to correct for multiple comparisons across the
614 brain (see Figure 5.C). This contrast shows the regions in which structural atrophy contributed
615 positively to higher predicted discounting in bvFTD than in controls (regions in red). These included
616 the OFC, anterior insulae, dorsal ACC, striatum, thalamus, amygdalae, hippocampus, and middle
617 temporal regions. These regions corresponded to areas combining the presence of negative weights
618 in the predictive brain pattern (i.e., voxels for which higher GMD predicts lower discounting and more
619 patient decision-making, shown in Figure 5.B) and the presence of significant grey matter atrophy due
620 to bvFTD pathology (see atrophy pattern in Figure 5.A). Thus, the contrast shown in Figure 5.C also
621 maps the regions in which the SIS is the most similar to bvFTD atrophy pattern.

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Figure 5. Spatial distribution of regions contributing to higher predicted discounting in bvFTD in Study 3. We computed an importance map as the unsummed matrix dot product between the Structural Impulsivity Signature (SIS) (developed in Study 1) and the individual grey matter density map of each Study 3 participant. Since higher resulting dot product contributes to higher predicted

628 | discounting, the importance map shows how brain regions contribute to increased (or decreased)
629 | predicted discounting in each individual. We performed a t-test contrasting bvFTD patients and
630 | controls (bvFTD > controls) on the resulting importance maps, to show in particular the regions in
631 | which the contribution to higher discounting was significantly higher in bvFTD than in controls. Within
632 | regions showing atrophy in bvFTD (see 6.A), those corresponding to negative (/positive) weights in the
633 | whole-brain predictive pattern (see 6.B) contributed to increase (/decrease) discounting in bvFTD (see
634 | 6.C). **(A)** VBM-derived grey matter atrophy map of bvFTD patients contrasted with matched controls
635 | (bvFTD<Controls), FWE-corrected and thresholded at $p < 0.05$. **(B)** Unthresholded whole-brain weight
636 | map of the structural brain pattern developed in Study 1 and used in Study 2 to predict delay
637 | discounting in bvFTD patients (N=24) and matched controls (N=18). Negative weights (contributing to
638 | lower discounting with higher grey matter density) are in blue and positive weights (contributing to
639 | higher discounting with higher grey matter density) are in orange. **(C)** Contrast between bvFTD
640 | patients and controls (bvFTD>Controls) on the importance map, FWE-corrected and thresholded at p
641 | < 0.05 ; this map shows regions contributing to increase discounting in bvFTD patients (compared to
642 | controls) in red and regions contributing to decrease discounting in bvFTD patients (compared to
643 | controls) in blue, the balance being in favor of a global increase in predicted discounting in bvFTD
644 | patients.

645 **DISCUSSION**

646

647 Impulsive and maladaptive decision-making is a transversal feature of many mental disorders,
648 especially prominent in behavioral-variant frontotemporal dementia (bvFTD). Yet, its relationship with
649 individual brain characteristics, in particular brain structure, is still debated. Here, we used a machine
650 learning technique to develop a brain signature (i.e., a multi-variate brain model) of individual
651 differences in delay discounting—a facet of impulsivity—based on whole-brain grey matter density
652 patterns. We performed out-of-sample cross-validation in a first sample of 117 healthy adults (Study 1)
653 used for brain signature development. We further tested the generalizability of this brain signature
654 developed in Study 1 in two independent studies: a second sample of 166 healthy adults (Study 2)
655 and a clinical study including 24 bvFTD patients and 18 matched controls (Study 3). Individual
656 differences of whole-brain grey matter density reliably predicted individual differences in discounting
657 rates in the first sample of healthy adults but not in the second independent sample. However, the
658 brain signature predicted individual differences of urgency (a subcomponent of impulsivity according to
659 the UPPS model) with small-to-moderate effect sizes in both the first and the second samples of
660 healthy adults. Most importantly, in the clinical study, we found that this structural signature of
661 impulsivity (SIS) separated bvFTD patients from controls with 81% accuracy and that it significantly
662 predicted not only individual differences in delay discounting across participants but also inhibition
663 deficit (objectively assessed from the Hayling test), even within the group of bvFTD patients. Thus, the
664 SIS might be more closely and reliably related to the broader concepts of impulsivity, urgency, and
665 inhibition deficits rather than to specifically delay discounting, which may be more driven by cultural
666 and educational factors than trait urgency. In sum, our results suggest that: 1) it is possible to predict
667 individual differences in impulsivity from whole-brain structure and 2) this novel brain signature is
668 sensitive to the structural atrophy that is characteristic of bvFTD, making it a novel candidate
669 neuromarker for improving bvFTD diagnosis.

670 The identification of the SIS advances our knowledge of the neurobiology underlying individual
671 differences in impulsivity. Higher discounting (i.e., greater impulsivity) was associated with higher grey
672 matter density in clusters of the lateral parietal and occipital cortex as well as in regions of the OFC,
673 vmPFC, ventral striatum, lateral PFC, precentral gyrus, and precuneus. Functional activation of these
674 regions during intertemporal choices and in response to rewards has previously been shown to predict

675 higher discounting^{14,52}. The SIS obtained from Study 1 also revealed regions in which greater grey
676 matter density contributes to lower individual impulsivity. Among the strongest negative contributors,
677 we found clusters corresponding to hub regions of the salience network (anterior insulae, dorsal ACC,
678 amygdalae). Dorsal ACC and anterior insula were also consistently found as significant regions
679 predicting delay discounting from whole-brain functional MRI¹⁴. These regions are associated with the
680 processing of emotionally significant internal and external stimuli^{51,53,54} and awareness of present and
681 future affective states⁵⁵; they are also supposed to be involved in switching between large-scale
682 networks to facilitate access to attention and working memory resources in the presence of a salient
683 event⁵⁶. These areas are also known to be involved in cognitive conflict processing^{57,58} and previous
684 studies have shown their response to difficult choices (characterized by choice conflicts between
685 options) during delay discounting⁵⁹. Thus, our results suggest that more impulsive individuals might
686 be those for whom lower affective, attentional, and conflict processing would lead to more impulsive
687 decision-making, favouring immediately rewarding options over long-term consequences of behavior.

688 The SIS has the potential to contribute to the early diagnosis of conditions characterized by
689 high impulsivity, such as bvFTD. Brain signatures can in particular help the diagnosis of conditions
690 involving brain lesions that are sometimes difficult to detect by mere visual inspection of MRI scans,
691 especially at early stages of the disease. In addition, brain signatures can constitute neuroimaging
692 markers with diagnostic value that can be used across different samples and populations^{11,60}. The SIS
693 may contribute to the diagnosis of bvFTD by complementing other brain models able to detect bvFTD.
694 A few previous studies successfully trained structural MRI classifiers for the specific purpose of
695 distinguishing FTD patients from controls (e.g.,⁶¹⁻⁶³). These bvFTD classifiers have shown their
696 accuracy to detect patients with clear structural brain damage but their ability to distinguish individuals
697 at risk of developing FTD due to genetic mutations is likely to be limited to the period just before
698 symptom onset^{64,65}. Under the hypothesis of a continuum of marked impulsivity in presymptomatic
699 individuals and patients¹⁶, the SIS might serve the early prediction and monitoring of bvFTD before
700 symptom onset. Impulsive behaviors may be present in an attenuated form long before clinical
701 diagnosis and hard to detect with traditional clinical methods. A neuromarker predicting impulsivity
702 may be sensitive to specific brain modifications that appear very early in individuals predisposed to
703 FTD (possibly as neurodevelopmental lesions⁶⁶) and would thus allow to enhance the monitoring of

704 clinical signs of these subtle behavioral changes. Future tests of this brain signature in
705 presymptomatic populations will allow to evaluate these potential clinical applications.

706 As it predicts nearly 30% of the variance of inhibition deficit among bvFTD patients, the SIS
707 may be sensitive to lesions in a structural network underlying the core bvFTD symptom of disinhibition.
708 In addition to its potential contribution to the early detection of presymptomatic individuals, this brain
709 signature may thus aid differential diagnosis and provide insight into the neuropsychological profiles of
710 patients. The SIS may for instance help to distinguish bvFTD from other neurodegenerative or
711 neuropsychiatric conditions with different core symptoms. The differential diagnosis of Alzheimer's
712 disease and bvFTD can in particular be challenging. Using neuromarkers such as the SIS in cases of
713 diagnostic uncertainty potentially impacting the choice of treatment could therefore be highly valuable
714 ⁶⁷ and should be an avenue for future studies. Moreover, the SIS could become a useful tool to
715 disentangle the phenotypic heterogeneity within bvFTD population ⁶⁸. The characterization of different
716 clinical and behavioral profiles within the bvFTD spectrum could help to better understand the
717 pathology, and to better adapt treatments according to patients' specific needs.

718 Despite holding promises for future clinical applications, we note that our results also point at
719 challenges in generalizing the brain signature to other independent samples of healthy adults. We
720 were successful at predicting delay discounting from whole-brain grey matter in a first rather
721 homogenous sample of healthy adults (male participants, controlled experimental conditions) showing
722 significant variability in terms of impulsivity and a positive correlation between the discounting rate and
723 urgency. In a second independent sample of healthy adults with lower variance of impulsivity and a
724 slightly negative correlation between the discounting rate and urgency, we could not replicate the
725 association with measured discounting rates but found evidence of the conceptual validity (i.e., a link
726 with the urgency trait) of brain-based predictions. This suggests that the variance captured by the SIS
727 developed in the first sample is more reliably related to individual differences in urgency than to
728 individual differences in discounting. The fact that urgency was slightly negatively correlated with the
729 discounting rate in the second healthy sample questions the idea that delay discounting necessarily
730 captures individual differences in impulsivity. These two constructs overlap but are not equivalent and
731 previous studies have already reported an absence of link between delay discounting and some
732 psychometric measures of impulsivity (e.g., ^{69,70}). Discounting rate is also a state-dependent variable
733 ⁷¹ and depends on situational factors such as cultural and social context ⁷². In addition, the links

734 between personality and discounting rates may depend on participants' cognitive abilities ⁷³.
735 Therefore, association between delay discounting and other measures of trait impulsivity may vary
736 according to samples and studies. A promising approach for future studies would therefore be to
737 predict latent variables that underlie different observed variables related to the same concept of
738 impulsivity (instead of only one observed variable such as the discounting rate), which might achieve
739 better performance in terms of replicability and generalizability ⁹. Although multivariate brain
740 signatures can be replicable with moderate sample sizes ⁷⁴, future studies aiming to develop brain
741 signatures of impulsivity could also benefit from using larger and more diverse samples ⁷⁵. More
742 generally, we note that our results suggest a relatively small contribution of interindividual variability in
743 brain structure to interindividual variability in impulsivity among healthy adults. Effect sizes of
744 associations between predicted and observed impulsivity are however in line with those reported for
745 most brain signatures of behavioral individual differences using structural features ⁹. Moreover, like
746 variability in brain structure, variability in genotype accounts for a rather small part of the variance of
747 impulsivity ⁷⁶. The magnitude of associations between brain structure and behaviors may be limited in
748 the general population but these associations might be more salient within populations with a marked
749 variability of both brain and behavior such as patients with neurodegenerative conditions.

750 In conclusion, our results advance our knowledge of the association between impulsivity and
751 brain structure in healthy adults and in patients with bvFTD. They also point at inherent challenges in
752 developing replicable and generalizable brain signatures of individual differences based on brain
753 structure. By identifying a structural network associated with individual differences in discounting rates,
754 our results provide insight into the potential neurobiological bases of trait impulsivity (and in particular
755 its urgency component). The good performance of the SIS among patients with bvFTD suggests a
756 possible continuum of brain-impulsivity relationship across healthy and clinical conditions. Most
757 noteworthy, the SIS separates bvFTD patients from controls with high accuracy, pointing at the
758 potential clinical value for the diagnosis of bvFTD, in particular for the purpose of stratifying this
759 heterogenous condition. MRI can be instrumental to confirm an FTD diagnosis ⁶⁷ and the SIS only
760 requires a preprocessed T1-weighted scan to reach a prediction. It holds promise as a phenotypic
761 marker in patients with neurodegenerative or psychiatric conditions associated with high impulsivity.
762 Future studies could test its clinical potential and whether this brain signature could be used in a real-
763 life patient workflow.

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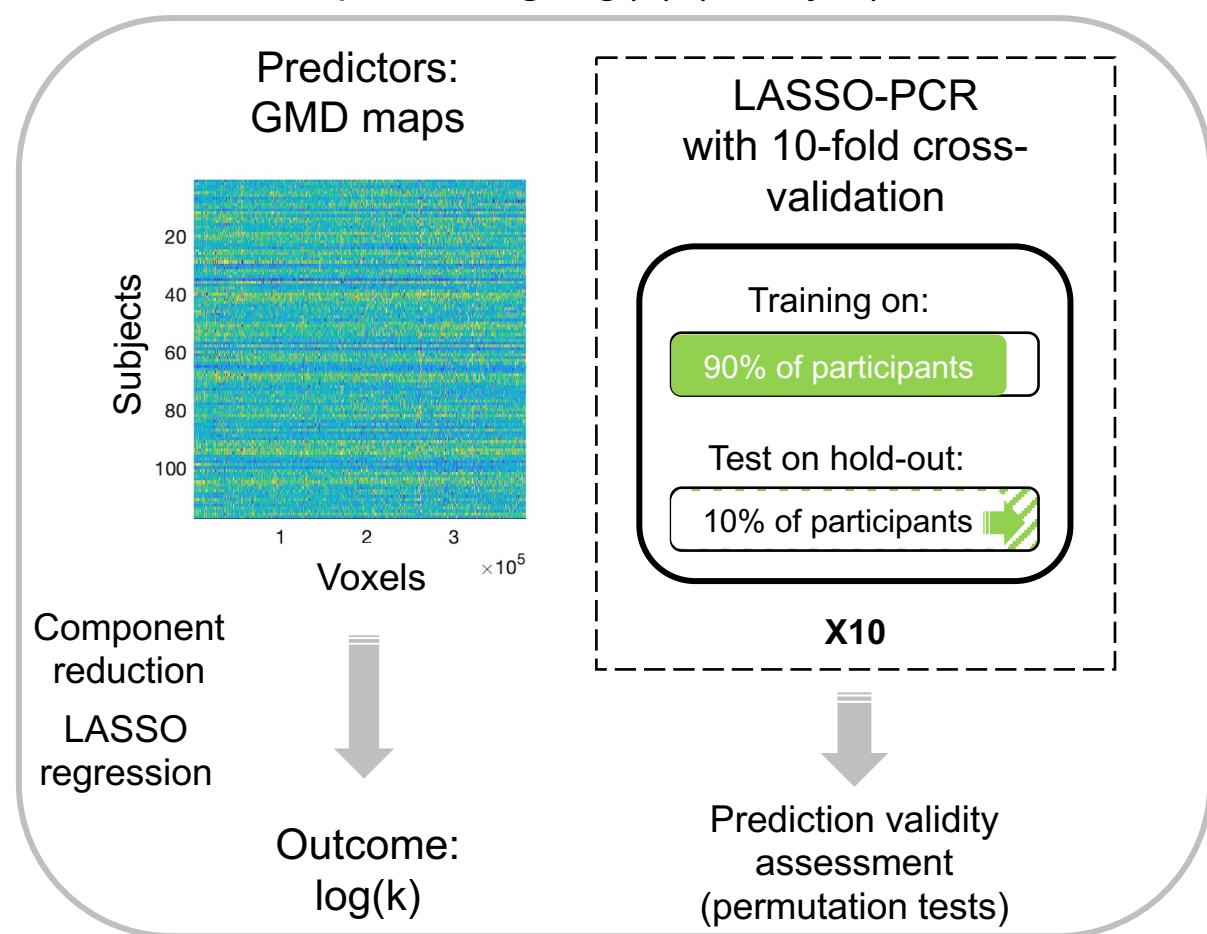
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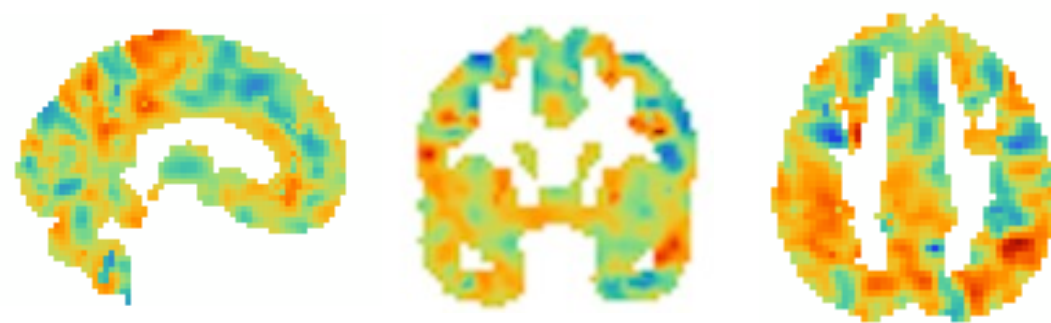
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A. General analytic approach

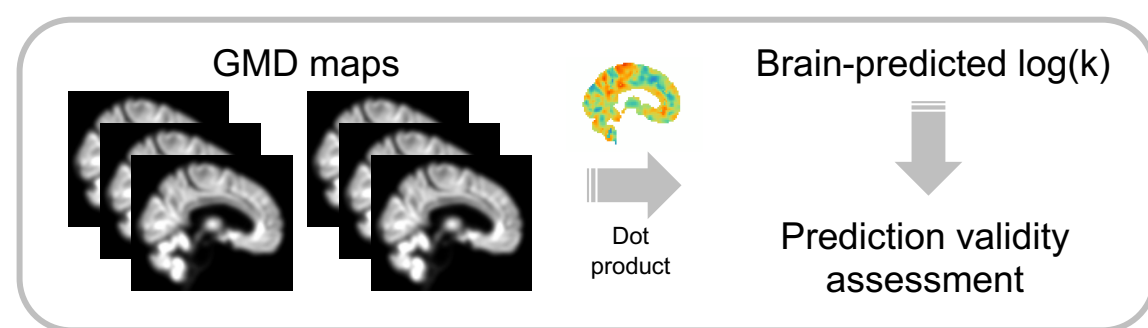
Development of a brain signature predicting $\log(k)$ (Study 1)



Resulting whole-brain pattern after voxel weight reconstruction



Application to new subjects in independent samples (Studies 2 & 3)



B. Delay discounting paradigms and prediction validity assessment

STUDY 1

N = 117 healthy adults (men)



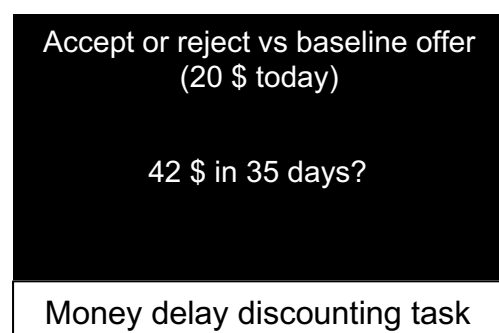
Actual $\log(k)$
Urgency trait (I-8)

Predicts ?

Brain-predicted $\log(k)$

STUDY 2

N = 166 healthy adults



Actual $\log(k)$
Urgency trait (UPPS)

Predicts ?

Brain-predicted $\log(k)$

STUDY 3

N = 24 bvFTD patients & 18 matched controls



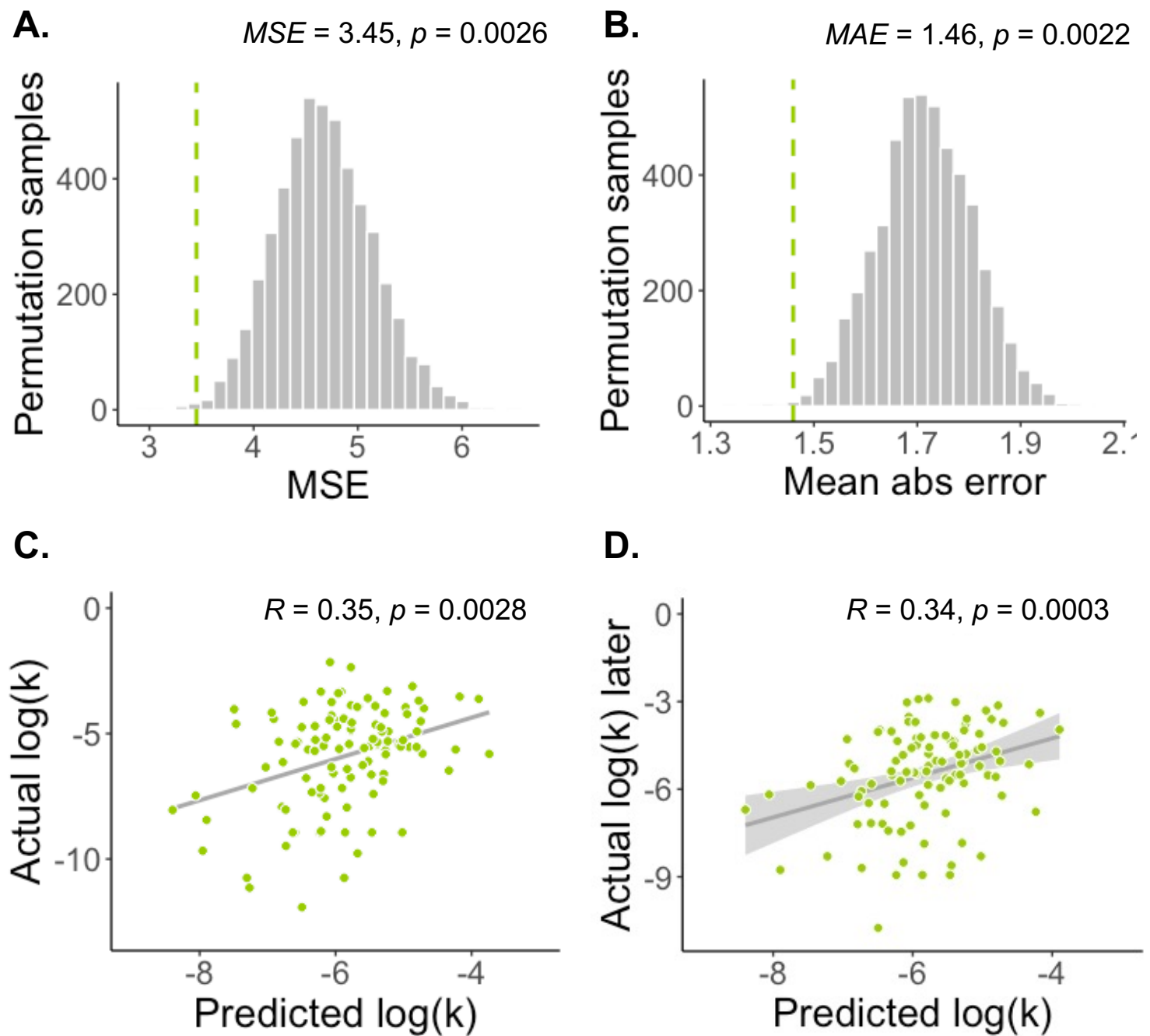
Actual $\log(k)$ money - Actual $\log(k)$ food
Patient vs Control
Patient's inhibition deficit & executive deficit

Predicts ?

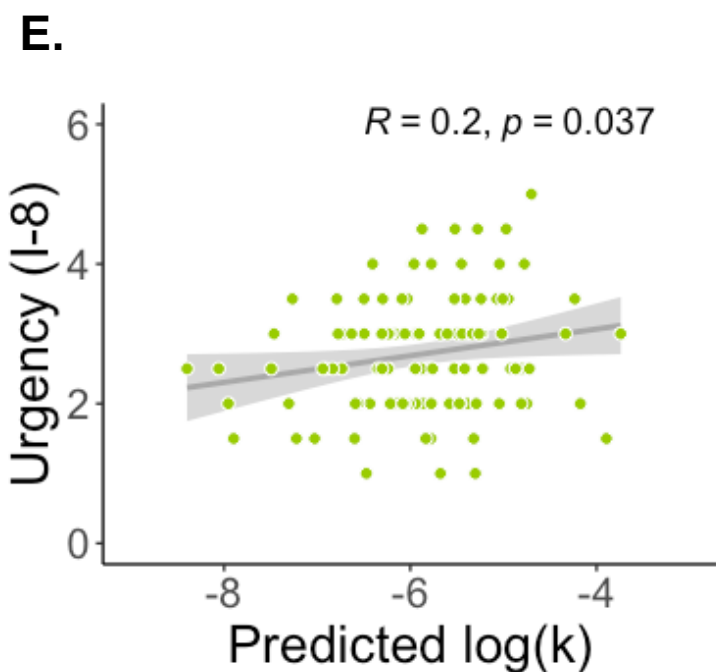
Brain-predicted $\log(k)$

Validity of brain-based predictions of impulsivity in healthy participants

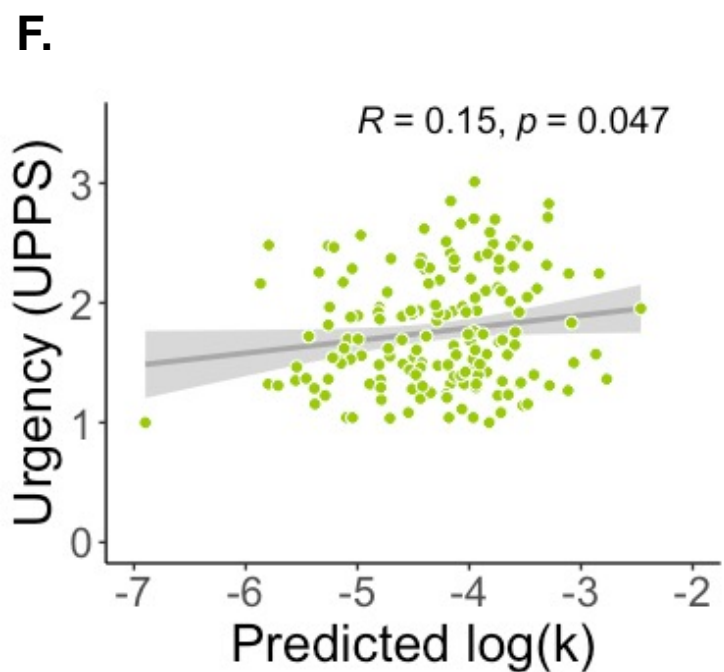
Study 1 – Prediction of delay discounting



Study 1 – Prediction of urgency

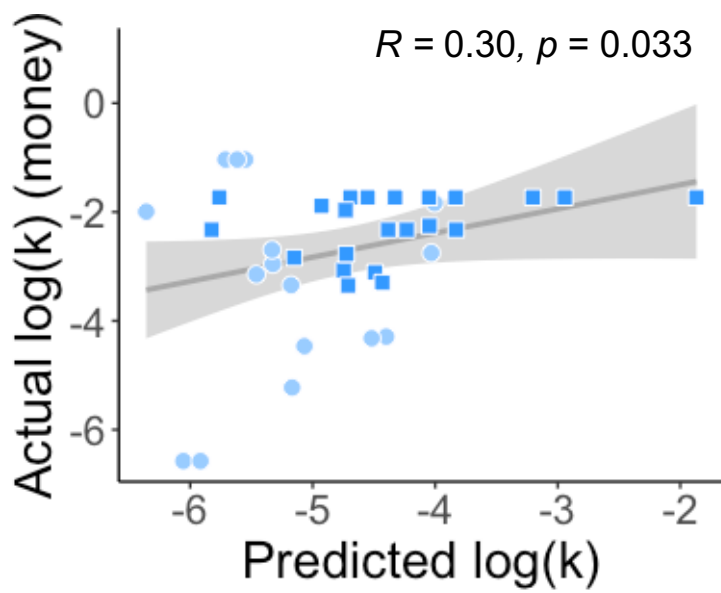


Study 2 – Prediction of urgency

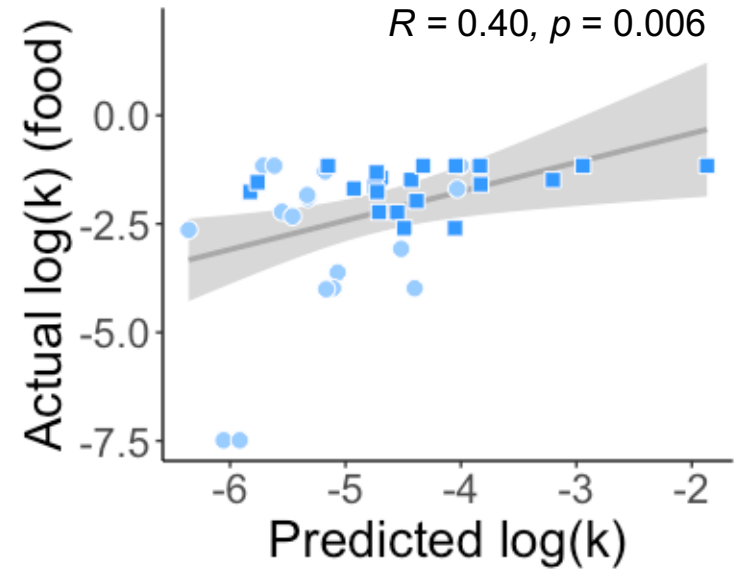


Validity of brain-based predictions of impulsivity in patients with bvFTD matched with controls (Study 3)

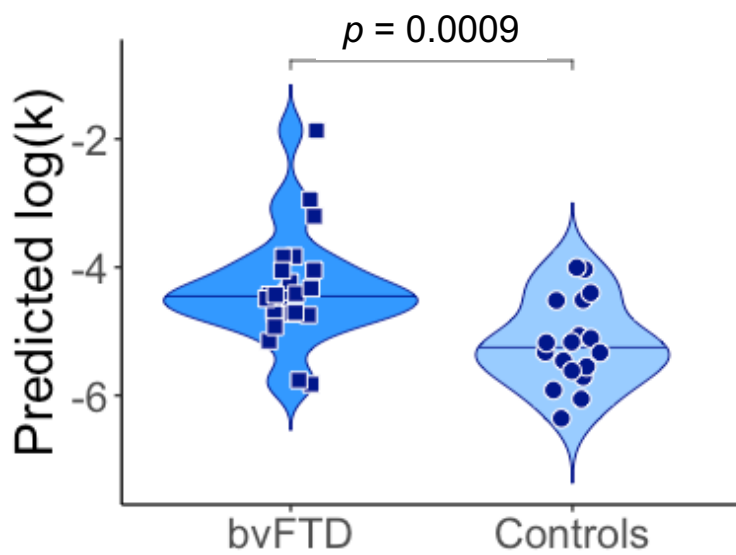
A.



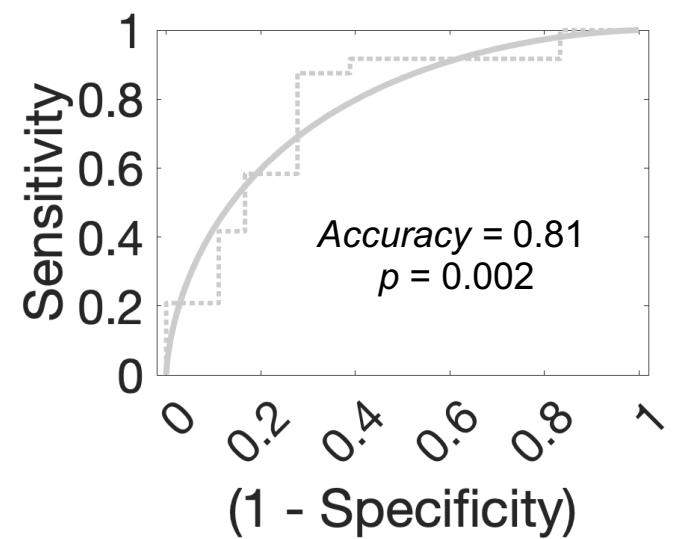
B.



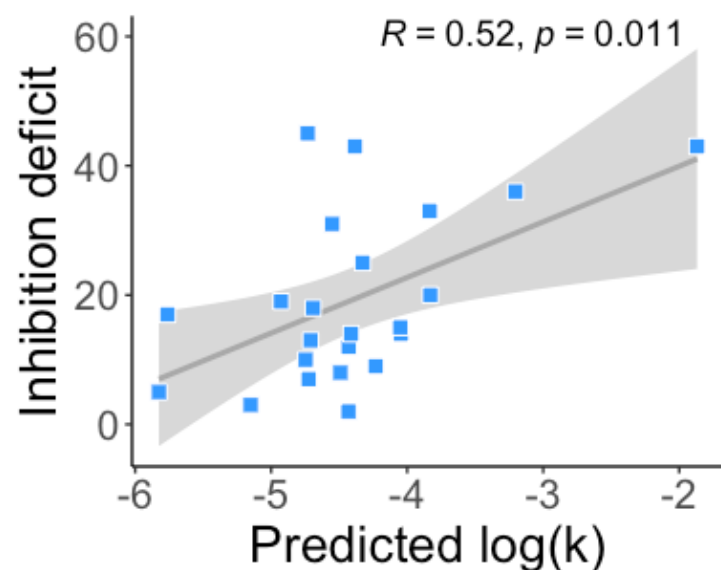
C.



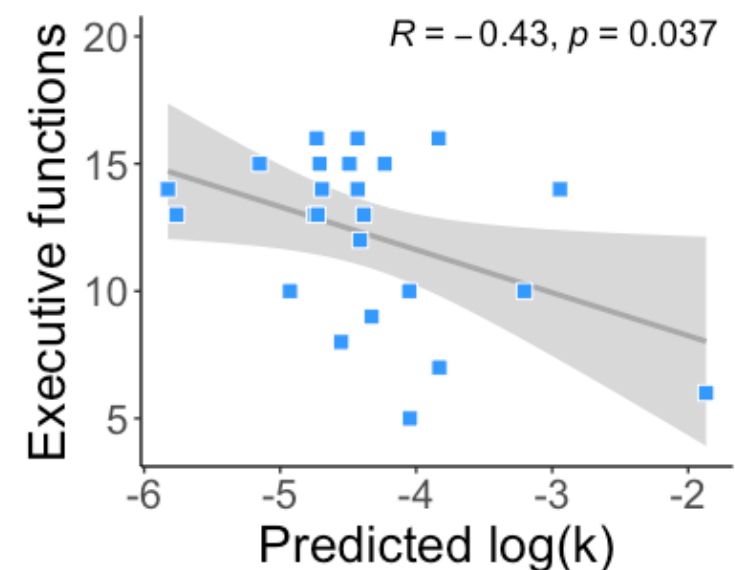
D.



E.

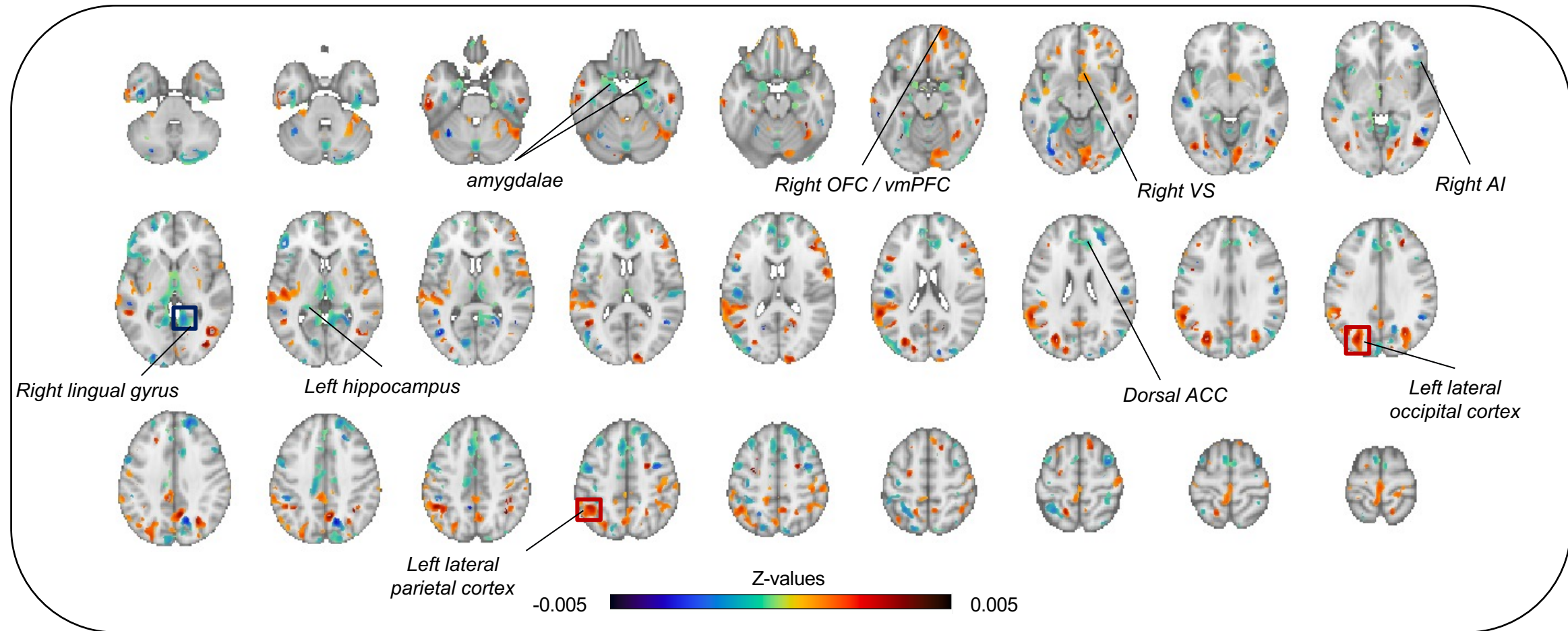


F.

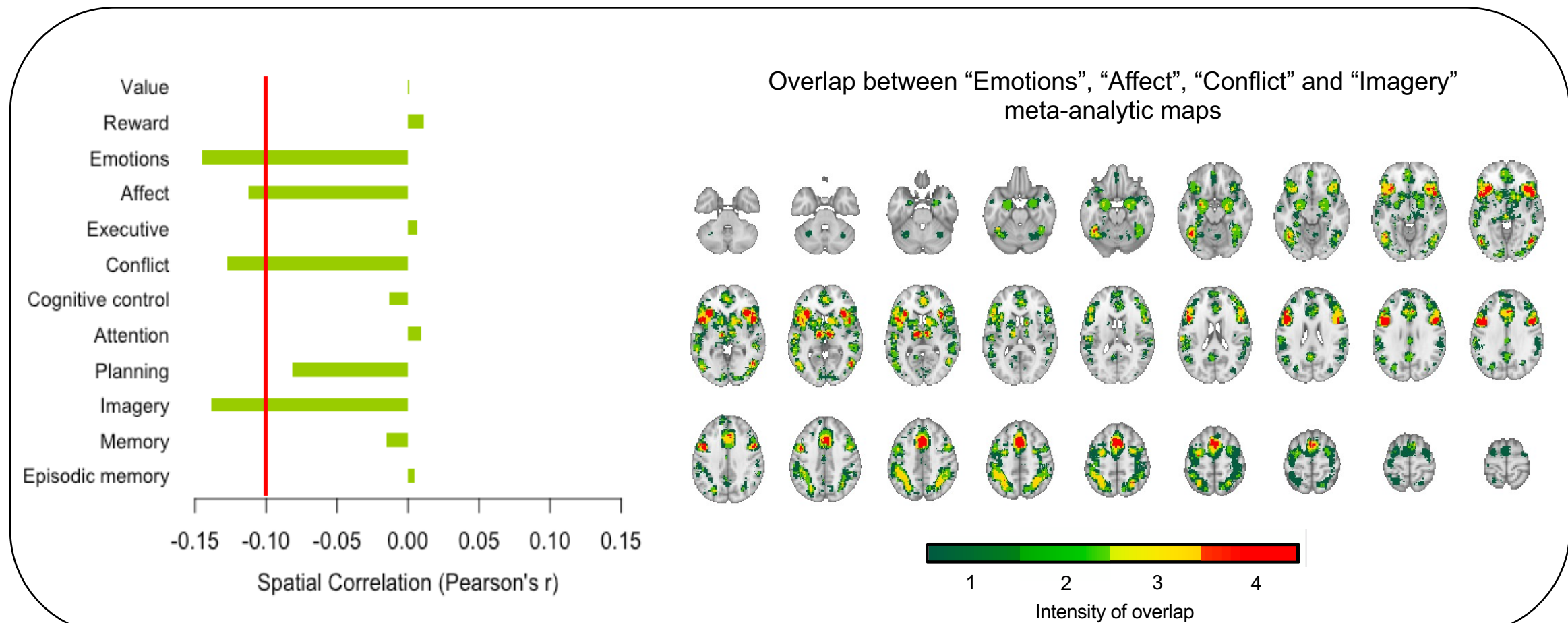


Study 1: Spatial distribution of weights in the structural brain pattern predicting delay discounting

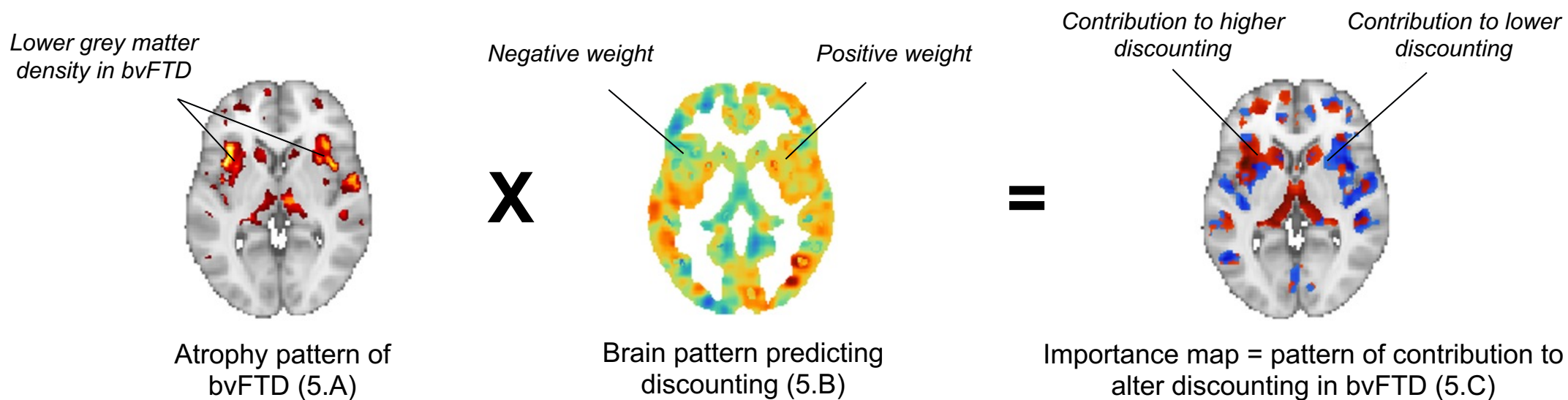
A. Thresholded weights of the brain pattern after bootstrapping



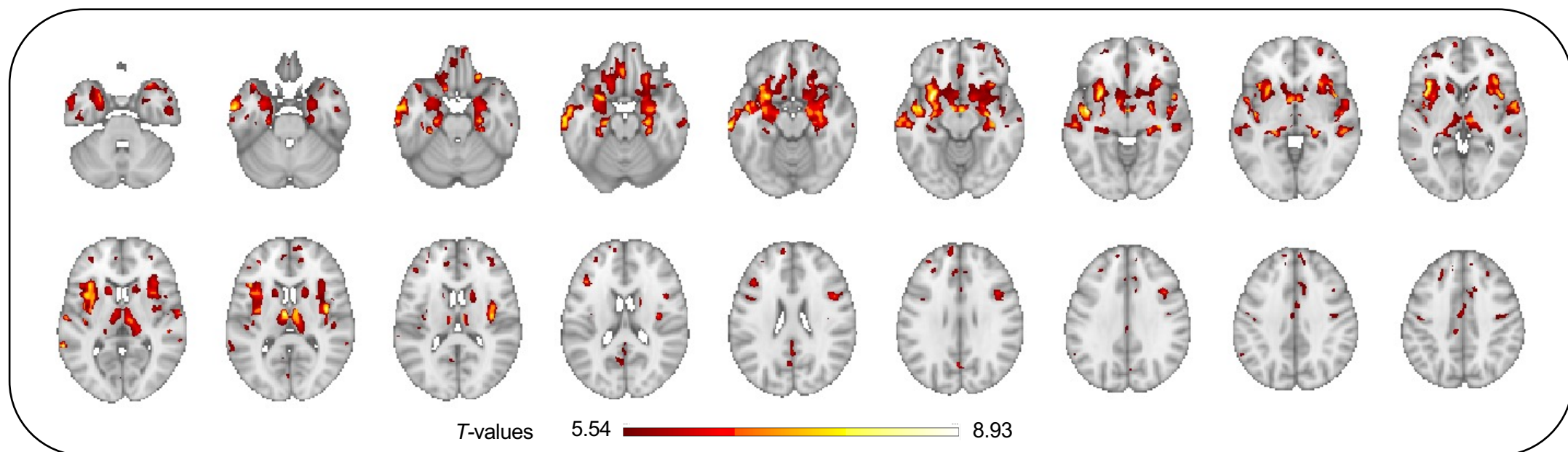
B. Spatial similarity of the brain pattern with meta-analytic maps



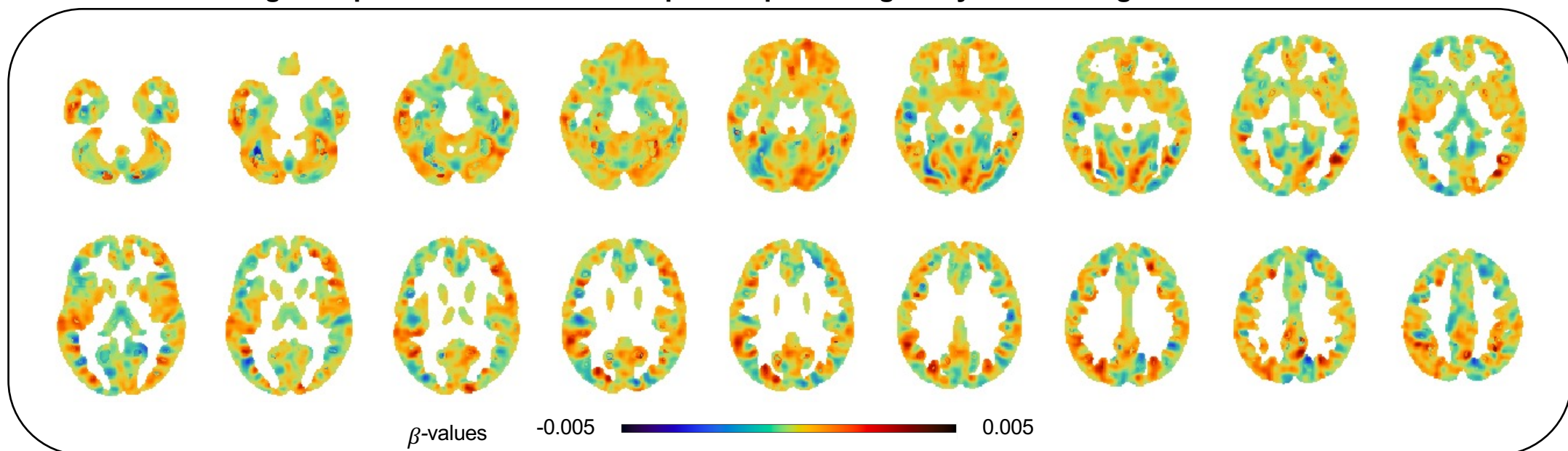
Study 3: Spatial distribution of brain regions contributing to higher predicted delay discounting in bvFTD patients



A. Thresholded *T*-map of bvFTD vs Controls contrast (bvFTD<Controls) on whole-brain grey matter density



B. Whole-brain weight map of the structural brain pattern predicting delay discounting



C. Thresholded *T*-map of bvFTD vs Controls contrast (bvFTD>Controls) on whole-brain importance map

