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Decoding with Confidence: Statistical Control on Decoder Maps

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Abstract

In brain imaging, decoding is widely used to infer relationships between brain and cognition, or to craft brain-imaging biomarkers of pathologies. Yet, standard decoding procedures do not come with statistical guarantees, and thus do not give confidence bounds to interpret the pattern maps that they produce. Indeed, in whole-brain decoding settings, the number of explanatory variables is much greater than the number of samples, hence classical statistical inference methodology cannot be applied. Specifically, the standard practice that consists in thresholding decoding maps is not a correct inference procedure. We contribute a new statistical-testing framework for this type of inference. To overcome the statistical inefficiency of voxel-level control, we generalize the Family Wise Error Rate (FWER) to account for a spatial tolerance δ , introducing the δ -Family Wise Error Rate (δ -FWER). Then, we present a decoding procedure that can control the δ -FWER: the Ensemble of Clustered Desparsified Lasso (EnCluDL), a procedure for multivariate statistical inference on high-dimensional structured data. We evaluate the statistical properties of EnCluDL with a thorough empirical study, along with three alternative procedures including decoder map thresholding. We show that EnCluDL exhibits the best recovery properties while ensuring the expected statistical control.

1 Introduction

Predicting behavior or diseases status from brain images is an important analytical approach for imaging neurosciences, as it provides an effective evaluation of the information carried by brain images. Machine learning tools, mostly supervised learning, are

indeed used on brain images to infer cognitive states [Haynes and Rees, 2006, Norman et al., 2006] or to perform diagnosis or prognosis [Demirci et al., 2008, Fan et al., 2008]. Brain images are obtained from MRI or PET imaging, or even EEG- or MEG-based volume-based activity reconstruction. They are used to predict a *target* outcome: binary (e.g., two-condition tasks), discrete (e.g., multiple-condition tasks) or continuous (e.g., age). The *decoding models* used for such predictions are most often linear models, characterized by a weight map that can be represented as a brain image [Mourao-Miranda et al., 2005, Varoquaux and Thirion, 2014].

Besides the prediction accuracy achieved, this estimated weight map is crucial to assess the information captured by the model. Typically, the produced weight maps are used to identify discriminative patterns [Haxby et al., 2001, Mourao-Miranda et al., 2005, Gramfort et al., 2013] and support reverse inferences [Poldrack, 2011, Schwartz et al., 2013, Varoquaux et al., 2018], *i.e.*, conclude on the implication of brain regions in the studied process.

Unlike in standard analysis —statistical parametric mapping [Poldrack et al., 2011, chap 7]—, in decoding the feature importance is tested *conditional on other brain features*, *i.e.*, it assesses whether each feature *adds* to information conveyed by other features. Weichwald et al. [2015] highlight the fact that decoding, *i.e.*, multivariate or conditional analysis, and encoding, *i.e.*, univariate or marginal analysis, are complementary. They notably argue that taking the two perspectives is essential for causal interpretation regarding the implication of brain regions in the target outcome (see also Haufe et al. [2014]).

While decoding optimizes the prediction of a target outcome, little or nothing can be concluded about the significant features of weight maps. Indeed, those maps do not come with well-controlled statistical properties, making decoding models hard to interpret. For instance, considering linear Support Vector Machines (SVM) [Cortes and Vapnik, 1995] or linear Support Vector Regression (SVR) [Smola and Schölkopf, 2004], that are popular in neuroimaging [Pereira et al., 2009, Rizk-Jackson et al., 2011], a natural way to recover predictive regions from their weight maps is to threshold these maps (e.g. Mourao-Miranda et al. [2005], Rehme et al. [2015], Sato et al. [2013], Lee et al. [2010]). However, this approach is problematic for two reasons: there exists no clear way to choose the threshold as a function of a desired significance, and it is unclear whether such a thresholded map is still an accurate predictor of the outcome. Solutions that bypass the arbitrary threshold choice have been proposed, such as Recursive Feature Elimination (RFE) [De Martino et al., 2008], but the produced maps still lack statistical guarantees.

In this work, we show that the natural procedure that consists in thresholding standard decoders, such as SVR, is not a relevant solution. In this respect, we consider two thresholding strategies: one that keeps extreme weights, and another one that computes the threshold by performing a permutation test. Unlike RFE, these two thresholding strategies can be derived from statistical testing considerations —yet, these statistical properties are not assumption free. We also consider decoders that provide confidence intervals around the estimated weight map. As detailed in the next section, these ap-

76 proaches also face severe challenges in terms of statistical power and computational
77 tractability. They have to rely on algorithmic shortcuts, approximations and hypotheses
78 that are more or less problematic in practice.

79 Hence, for all methods considered, the control of false detections is only achieved
80 within a certain theoretical framework, and given a series of assumptions that are not
81 easily checked. It is thus fundamental to analyze their statistical behavior with an
82 extensive empirical study. We present here a set of experiments assessing the accuracy
83 of the error rate control and support recovery on real and semi-synthetic brain-imaging
84 data.

85 Additionally, to achieve a reasonable compromise between error control and power,
86 we introduce a new type of error control adapted to imaging problems. The proposed
87 quantity is a generalization of the Family Wise Error Rate (FWER) [Hochberg and
88 Tamhane, 1987] including a spatial tolerance parametrized by a distance δ . We call it
89 δ -FWER.

90 In Section 2, we bring useful background, discuss the statistical guarantees that we
91 aim at for pattern maps, and make the theoretical and practical inference challenges
92 explicit. In Section 3 we provide a definition of the δ -FWER along with a geometrical
93 interpretation of this quantity. We also describe several statistical inference methods
94 producing statistical maps reflecting the significance of conditional association of brain
95 regions with a target, while controlling the FWER or δ -FWER. Section 4 and Section 5
96 follow with extensive experiments on simulations and large-scale fMRI datasets that
97 study the behavior of the benchmarked solutions regarding false positive control and
98 recovery.

99 2 Context: decoding-map recovery

100 In this section, we first review a result due to Weichwald et al. [2015] about the com-
101 plementarity of univariate and multivariate inference, then we present the statistical
102 guarantees that we aim at for on brain-wide decoding maps, lastly we formalize the
103 problem of statistical inference on such maps.

104 2.1 Complementarity of univariate and multivariate inference

105 Statistical inference in neuroimaging can be performed using a mass univariate model-
106 ing, *i.e.*, fitting brain activity maps from an outcome —leading to *encoding models*—
107 or by predicting an outcome from brain maps using multivariate modeling —leading to
108 *decoding models*. The complementarity of univariate and multivariate analyses has been
109 demonstrated in Weichwald et al. [2015]. Specifically, they argued: “We showed that only
110 encoding models in a stimulus-based setting support unambiguous causal statements.
111 This result appears to imply that decoding models, despite their gaining popularity in
112 neuroimaging, are of little value for investigating the neural causes of cognition. In the
113 following, we argue that this is not the case. Specifically, we show that by combining
114 encoding and decoding models, we gain insights into causal structure that are not pos-

115 sible by investigating each type of model individually.” This statement clearly implies
 116 that inference tools are needed for multivariate analysis. The present work is thus fully
 117 dedicated to multivariate inference. We simply provide some univariate inference results
 118 for reference, given that they address different yet complementary questions.

119 2.2 Statistical control with spatial tolerance

120 In decoding, the signals from voxels are used concurrently to predict an outcome. Given
 121 that they display high correlations, trying to identify the effect of each covariate (voxel)
 122 is not possible. Precise voxel-level control may not be necessary: current brain models
 123 are rather specified at a regional scale, see *e.g.*, [Glasser et al., 2016]. Additionally, to
 124 control a statistical error, detecting a voxel adjacent to a truly predictive region is less
 125 problematic than detecting a false positive far from such a predictive region. These
 126 two facts argue in favor of incorporating a spatial tolerance in the sought statistical
 127 control, as with efforts in standard analysis [Smith and Nichols, 2009, Da Mota et al.,
 128 2014, Bowring et al., 2019]. Hence, we introduce a generalization of the Family Wise
 129 Error Rate (FWER) [Hochberg and Tamhane, 1987]: the δ -FWER. This generalization
 130 is related to the extension of the False Discovery Rate (FDR) [Benjamini and Hochberg,
 131 1995] proposed by Nguyen et al. [2019] and Gimenez and Zou [2019], called δ -FDR and
 132 local-FDR, respectively.

133 2.3 Formal problem setting

134 **Notation.** For clarity, we use bold lowercase for vectors and bold uppercase for ma-
 135 trices. For $p \in \mathbb{N}$, we write $[p]$ for the set $\{1, \dots, p\}$. For a vector \mathbf{w} , \mathbf{w}_j refers to its j -th
 136 coordinate. For a matrix \mathbf{X} , $\mathbf{X}_{i,j}$ refers to the element in the i -th row and j -th column.

137 **Formalizing the decoding problem.** The target (outcome to decode) is observed in
 138 n samples and denoted by $\mathbf{y} \in \mathbb{R}^n$ (\mathbf{y} can be binary, discrete or continuous). The brain
 139 volume is discretized into p voxels. The corresponding p voxel signals are also referred
 140 to as explanatory variables, covariates or features. We denote by $\mathbf{X} \in \mathbb{R}^{n \times p}$ the matrix
 141 containing (column-wise) the p covariates $\{\mathbf{X}_1, \dots, \mathbf{X}_p\}$. We assume that, for all $i \in [n]$,
 142 the samples $(\mathbf{y}_i, \mathbf{X}_{i,\cdot})$ are i.i.d. Then, further assuming a linear dependency between the
 143 covariates and the response, the generative model is as follows:

$$\mathbf{y} = \mathbf{X}\mathbf{w}^* + \boldsymbol{\varepsilon} \quad , \quad (1)$$

144 where $\mathbf{w}^* \in \mathbb{R}^p$ is the true weight map and $\boldsymbol{\varepsilon}$ is the noise vector. In the present study,
 145 we assume for simplicity that the noise is Gaussian, *i.e.*, $\boldsymbol{\varepsilon} \sim \mathcal{N}(\mathbf{0}, \sigma_\varepsilon^2 \mathbf{I}_n)$, but extension
 146 to sub-Gaussian noise is possible.

147 **High dimensionality and structure of the data.** Given \mathbf{X} and \mathbf{y} , a standard
 148 procedure computes an estimate $\hat{\mathbf{w}}$ of \mathbf{w}^* . Getting statistical guarantees on \mathbf{w}_j^* , $j \in [p]$,
 149 means assessing with some degree of uncertainty that \mathbf{w}_j^* is non-zero, or equivalently,

150 giving a confidence interval for \mathbf{w}_j^* . This is hard in high dimension and when short-
151 and long-range correlations are present in the data. Indeed, for brain imaging data, n
152 is typically hundreds (or less), whereas p may amount to hundreds of thousands. In
153 addition, voxel signals are highly correlated, which makes model identification harder
154 due to multicollinearity and ill-posedness. Theoretical studies, *e.g.*, [Wainwright \[2009\]](#),
155 have revealed that in such settings there is no hope to *recover* completely and accurately
156 the predictive regions.

157 2.4 Current practices: thresholding decoding maps

158 **Uniform threshold.** Probably the most natural procedure used to recover discrimi-
159 native patterns is to threshold decoders with high prediction performance—a popular
160 choice is the linear SVM/SVR decoder [[Pereira et al., 2009](#), [Rizk-Jackson et al., 2011](#)].
161 Thresholding decoder maps at a uniform value—*i.e.*, the threshold is the same for all
162 weights—is probably the most common practice in neuroimaging; threshold value being
163 generally arbitrary: "naked-eye criteria". It is not thought of as a statistical operation,
164 and is sometimes left to the reader, who is presented unthresholded maps and yet told
165 to interpret only the salient features of these maps.

166 Permutation testing can also be used to derive a uniform threshold with explicit guar-
167 antees. The classical Westfall-Young permutation test procedure [[Westfall and Young,](#)
168 [1993](#)] is well-known in the univariate context to control the FWER [[Anderson, 2001](#)],
169 but its application to multivariate testing is not as straightforward. Then, instead of
170 considering the usual t -statistics, a permutation test can use the linear SVR weights.
171 An estimated weight map must be computed for the original problem and for several
172 permuted problems before performing the Westfall-Young procedure; this method is
173 detailed in [Sec. 3.3](#).

174 Under some assumptions (see [Sec. 3.2](#) and [Sec. 3.3](#)) that are more or less problematic
175 in practice, the uniform thresholding strategies might recover the predictive patterns
176 with FWER control. However, we will see that these naive strategies are not satisfactory
177 in practice.

178 **Non-uniform threshold.** Another method proposed by [Gaonkar and Davatzikos](#)
179 [\[2012\]](#), specifically designed for neuroimaging settings, relies on the analytic approxima-
180 tion of a permutation test performed over a linear SVM/SVR estimator. This method
181 computes confidence intervals around the weights of the proposed estimator. Then, un-
182 der some assumptions (see [Sec. 3.4](#)) that are not always met in practice, this procedure
183 controls the FWER. It is almost equivalent to thresholding the SVR weights with a
184 non-uniform threshold—*i.e.*, the threshold is specific to each weight. We refer to it as
185 Adaptive Permutation Threshold SVR (Ada-SVR) from now on.

186 2.5 Building decoders designed for statistical control

187 **Dimension reduction by voxel grouping.** A computationally attractive solution to
188 alleviate high dimensionality is to leverage the data structure and group adjacent—and

189 correlated— voxels, producing a closely related, yet compressed version of the original
 190 problem. In decoding, the grouping of voxels via spatially-constrained clustering algo-
 191 rithms has already been used to reduce the problem dimension [Gramfort et al., 2012,
 192 Varoquaux et al., 2012, Wang et al., 2015]. Specifically, groups of contiguous voxels can
 193 be replaced by the average signal they carry, reducing the dimensionality while improv-
 194 ing the conditioning of the estimation problem. However, such a compression introduces
 195 a bias, as the patterns are constrained by the clusters shape. This bias is problem-
 196 atic as there is no unique grouping or clustering of the voxels [Thirion et al., 2014]:
 197 many different groupings capture the signal as accurately. One way to mitigate this
 198 bias is to use aggregation of models [Breiman, 1996, Zhou, 2012] obtained from several
 199 voxel groupings. Varoquaux et al. [2012] implemented this idea by computing different
 200 groupings from different random subsamples of the full data sample. The corresponding
 201 procedure yields decoders with more stable maps as well as a better prediction accuracy.
 202 In this subsampling spirit, random subspace methods [Ho, 1998, Kuncheva et al., 2010,
 203 Kuncheva and Rodríguez, 2010] also improve the prediction accuracy with more stable
 204 solutions—but in this case the subsampling is performed on the raw features. More re-
 205 cently, a procedure, *Fast Regularized Ensembles of Models* (FReM) [Hoyos-Idrobo et al.,
 206 2018], has combined clustering and ensembling to reduce the variance of the weight map,
 207 while ensuring high prediction accuracy. Yet, FReM weight maps do not enjoy statistical
 208 guarantees.

209 **High-dimensional statistics tools.** There have been a variety of procedures to pro-
 210 duce p-value maps (map of p-values associated to every covariate) for linear models in
 211 high dimension [Wasserman and Roeder, 2009, Meinshausen et al., 2009, Bühlmann,
 212 2013, Zhang and Zhang, 2014, Javanmard and Montanari, 2014]. Yet, they are not di-
 213 rectly applicable to brain-imaging settings, as the dimensionality is too high. Based on a
 214 comparative review of those procedures [Dezeure et al., 2015], we have focused on the so-
 215 called Desparsified Lasso (DL), introduced in Zhang and Zhang [2014] and thoroughly
 216 analyzed by van de Geer et al. [2014]. Roughly, Desparsified Lasso can be seen as a
 217 Lasso-type [Tibshirani, 1996] extension of the least-squares to high dimensional settings,
 218 producing weight maps with well-controlled statistical distribution.

219 However, when the number p of features is much greater than the number n of
 220 samples, Desparsified Lasso lacks statistical power [Chevalier et al., 2018] and the com-
 221 putational cost becomes prohibitive. Indeed, solving Desparsified Lasso entails solving p
 222 Lasso problems with a design matrix $\mathbf{X} \in \mathbb{R}^{n \times p}$. Using the standard coordinate descent
 223 implementation [Friedman et al., 2007] the computation time is $\mathcal{O}(Tnp^2)$, with T the
 224 number of epochs used to solve the Lasso. However, when p is of order of few thou-
 225 sands and n few hundreds, Desparsified Lasso remains feasible with modest computer
 226 resources. In this context, the recently proposed Ensemble of Clustered Desparsified
 227 Lasso (EnCluDL) [Chevalier et al., 2018] combines three steps: a clustering procedure
 228 that reduces the problem dimension but preserves data structure, the Desparsified Lasso
 229 procedure that is tractable on the compressed problem, and an ensembling method intro-
 230 duced by Meinshausen et al. [2009] that aggregates several solutions of the compressed

231 problem. This method, summarized in [Sec. 3.5](#), follows a scheme similar to FReM but
 232 the inference and ensembling procedures are different since it aims at producing p-value
 233 maps with statistical properties. Indeed, under some assumptions (see [Sec. 3.5](#)), it can
 234 be shown that EnCluDL controls the δ -FWER at the desired nominal level.

235 Finally, Knockoff filters [[Barber and Candès, 2015](#), [Candès et al., 2018](#)], extended to
 236 work on images by [Nguyen et al. \[2019\]](#), are also an appealing procedure, though they
 237 can only control the FDR [[Barber and Candès, 2015](#)] or a relaxed version of the FWER
 238 [[Janson and Su, 2016](#)] incompatible with our spatial control, the δ -FWER detailed be-
 239 low. In this study, following the previous work of [Chevalier et al. \[2018\]](#), we focus on
 240 FWER or δ -FWER control. We then defer the extension of EnCluDL to FDR-controlling
 241 procedures and the benchmarking with alternatives to future work.

242 3 Materials and methods

243 3.1 δ -Family Wise Error Rate (δ -FWER)

244 In this section, we introduce a new way of controlling false detections that is well suited
 245 for neuroimaging settings as it incorporates spatial tolerance.

246 **True support under linear model assumption.** When considering multivariate
 247 inference, the *support* $S \subset [p]$ is the set of covariates that are non-independent of \mathbf{y}
 248 conditionally to the other covariates. The rest of the voxels form the *null region* N
 249 *i.e.*, $N = [p] \setminus S$. Formally, S is the unique set that verifies:

$$\begin{aligned} \forall j \in S, \quad \mathbf{X}_j \not\perp \mathbf{y} \mid \{\mathbf{X}_k, k \in [p] \setminus \{j\}\} , \\ \forall j \in N, \quad \mathbf{X}_j \perp \mathbf{y} \mid \{\mathbf{X}_k, k \in S\} , \end{aligned} \tag{2}$$

250 where the sign \perp denotes independence. Under the linear assumption made in (1), S
 251 becomes simply the set of non zero weights and N the set of zero weights:

$$\begin{aligned} S &= \{j \in [p] : w_j^* \neq 0\} , \\ N &= \{j \in [p] : w_j^* = 0\} . \end{aligned} \tag{3}$$

252 **δ -neighborhood.** The variables $\mathbf{X}_1, \mathbf{X}_2, \dots, \mathbf{X}_p$ can also be characterized by the spa-
 253 tial proximity of their underlying voxels in brain space: given $\delta \geq 0$, a voxel $k \in [p]$ is in
 254 the δ -neighborhood of a voxel (or a set of voxels) if their distance is less than δ .

255 **δ -null region.** For $\delta \geq 0$, we denote by $S^{(\delta)}$ the δ -dilation of the support S , *i.e.*, the
 256 set of voxels in S or in its δ -neighborhood. By definition, $S \subset S^{(\delta)}$. We denote by
 257 $N^{(-\delta)}$ the δ -erosion (inverse operation of a δ -dilation) of the null region N , implying
 258 that $N^{(-\delta)} \subset N$. From the definition of N we have immediately:

$$N^{(-\delta)} = [p] \setminus S^{(\delta)} , \tag{4}$$

259 We refer to $N^{(-\delta)}$ as the δ -null region. As shown in Fig. 1, we interpret the δ -null region
 260 as the subset of the covariates which are at a distance less than δ from the support
 261 covariates. We also give a practical example of the δ -null region in the case of real fMRI
 262 data in appendix in Fig. 14.

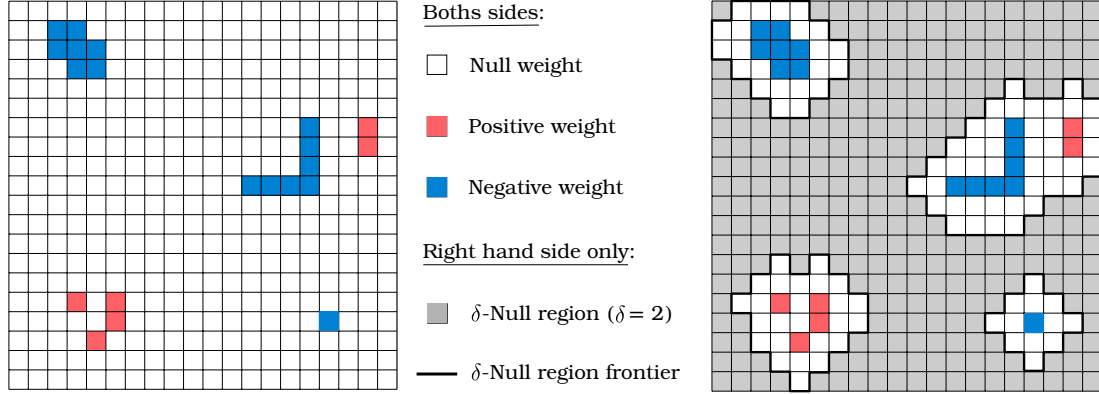


Figure 1: **Spatial tolerance to false discoveries.** Left: example of 2D-weight map, small squares represent voxels. The map is sparse. Right: representation of the δ -null region for the associated map with $\delta = 2$. The covariates in the δ -null region are "far" from non-null covariates, discoveries in this area are highly undesired. Discovering a null covariate "close" to a non-null covariate is tolerated.

263 **δ -Family Wise Error Rate (δ -FWER).** If we have an estimate of the support
 264 $\hat{S} \subset [p]$, we recall that the Family Wise Error Rate (FWER) is defined as the probability
 265 of making a false detection [Hochberg and Tamhane, 1987]:

$$\text{FWER}(\hat{S}) = \mathbb{P}(\hat{S} \cap N \neq \emptyset) . \quad (5)$$

266 Similarly, given $\delta \geq 0$, we defined the δ -FWER to be

$$\delta\text{-FWER}(\hat{S}) = \mathbb{P}(\hat{S} \cap N^{(-\delta)} \neq \emptyset) , \quad (6)$$

267 *i.e.*, the probability of making a detection at distance more than δ from the true support.
 268 The δ -FWER control is thus weaker than the FWER control, except when $\delta = 0$ and
 269 when the true support is empty (*i.e.*, $N = [p]$), in which case the δ -FWER coincides
 270 with the classical FWER.

271 3.2 Thresholded SVR (Thr-SVR)

272 In this section, we introduce Thresholded SVR (Thr-SVR), a procedure that thresholds
 273 uniformly the estimated SVR weight map, keeping extreme weights; this method corre-
 274 sponds to the most standard and simple approach to recover predictive patterns. The
 275 first step is to derive the SVR weights $\hat{\mathbf{w}}^{\text{SVR}}$. Then, assuming that the estimated weights

276 of the null region are sampled from a given distribution centered on 0, the corresponding
 277 standard deviation σ_{SVR} can be approximated with the following estimator:

$$\hat{\sigma}_{\text{SVR}} = \sqrt{\frac{1}{p} \sum_{j=1}^p (\hat{\mathbf{w}}_j^{\text{SVR}})^2} . \quad (7)$$

278 We could also consider other estimators to approximate this quantity (*e.g.*, [Schwartzman
 279 et al. \[2009\]](#)) but the former is simple and at worst biased upward when the support is
 280 not empty. Now, assuming a Gaussian distribution for the SVR weights in the null
 281 region, *i.e.*, for $j \in N$:

$$\hat{\mathbf{w}}_j^{\text{SVR}} \sim \mathcal{N}(0, \sigma_{\text{SVR}}^2) , \quad (8)$$

282 we can produce (corrected) p-values by applying a Bonferroni correction. The produced
 283 p-values are at worst conservative under the two assumptions discussed in [Section 6](#).
 284 In this procedure, the regression method considered is a linear SVR but similar results
 285 were obtained with other procedures (*e.g.*, Ridge regression).

286 3.3 Permutation Test SVR (Perm-SVR)

287 Now, we introduce another uniform thresholding strategy of SVR weights based upon a
 288 permutation test procedure. To derive corrected p-values from a permutation test, we
 289 first regress the design matrix against the response vector using a linear SVR to obtain
 290 an estimate $\hat{\mathbf{w}}^{\text{SVR}}$ of the weights map similarly as made in the Thr-SVR procedure.
 291 Then, permuting randomly R times the response vector and regressing the design matrix
 292 against the permuted response by a linear SVR, we obtain R maps $(\hat{\mathbf{w}}^{\text{SVR},(r)})_{r \in [R]}$.
 293 We can now apply the Westfall-Young step-down maxT adjusted p-values algorithm
 294 [[Westfall and Young, 1993](#), p. 116-117] taking the raw SVR weights instead of the usual
 295 t -statistics to derive the corrected p-values. A sufficient assumption to ensure the validity
 296 of the p-values is the pivotality of the SVR weights. Keeping the corrected p-values that
 297 are less than a given significance level —equal to 10% in this study— this procedure is
 298 equivalent to thresholding the SVR weight map. We call this procedure Permutation Test
 299 SVR (Perm-SVR). The only difference between Perm-SVR and the Thr-SVR procedure
 300 is the way of computing the threshold. To perform the permutation test procedure, we
 301 took $R = 1000$ permutations.

302 3.4 Adaptive Permutation Threshold SVR (Ada-SVR)

303 Here, we introduce Adaptive Permutation Threshold SVR (Ada-SVR), a statistical in-
 304 ference procedure that produces a weight map and confidence intervals around it; it is
 305 also almost equivalent to thresholding the SVR weights non-uniformly. Ada-SVR was
 306 first presented by [Gaonkar and Davatzikos \[2012\]](#). First, the authors derived an esti-
 307 mated weight $\hat{\mathbf{w}}^{\text{APT}}$ linearly related to the target by approximating the hard margin
 308 SVM formulation, their estimator is given by the following equation:

$$\hat{\mathbf{w}}^{\text{APT}} = \mathbf{L} \mathbf{y} , \quad (9)$$

309 where \mathbf{y} is the target variable and $\mathbf{L} \in \mathbb{R}^{p \times n}$ only depends on the design matrix \mathbf{X} :

$$\mathbf{L} = \mathbf{X}^\top \left[(\mathbf{X}\mathbf{X}^\top)^{-1} - (\mathbf{X}\mathbf{X}^\top)^{-1} \mathbf{1} (\mathbf{1}^\top (\mathbf{X}\mathbf{X}^\top)^{-1} \mathbf{1})^{-1} \mathbf{1}^\top (\mathbf{X}\mathbf{X}^\top)^{-1} \right], \quad (10)$$

310 where $\mathbf{1} \in \mathbb{R}^n$ is a vector of ones. The approximation made by (9) is notably valid under
 311 the assumption that all the data samples are support vectors, which might hold at least
 312 if $n \ll p$. Then, if \mathbf{y} is standardized and if n is large enough (so that the central limit
 313 theorem holds), one expects that under the null hypothesis for the j -th covariate:

$$\hat{\mathbf{w}}_j^{\text{APT}} \sim \mathcal{N}\left(0, \sum_{k=1}^n \mathbf{L}_{j,k}^2\right). \quad (11)$$

314 From (11), p-values can be computed and corrected by applying a Bonferroni correction
 315 (multiplying the raw p-values by a factor p).

316 3.5 Ensemble of Clustered Desparsified Lasso Algorithm (EnCluDL)

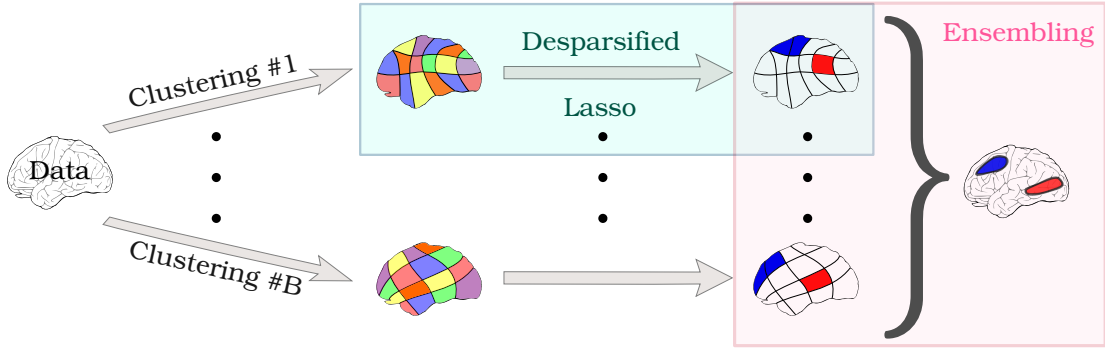


Figure 2: **Ensemble of Clustered Desparsified Lasso (EnCluDL) algorithm.** The EnCluDL algorithm combines three algorithmic steps: a clustering (or parcellation) procedure applied to images, the Desparsified Lasso procedure (statistical inference) to derive statistical maps, and an ensembling method that synthesizes several statistical maps. In the first step, B clusterings of voxels are generated using B random subsamples of the original sample. Then, for each grouping-based data reduction, a statistical inference procedure is run resulting in B z-score maps (or p-value maps). Finally, these maps are ensembled into a final z-score map using an aggregation method that preserves statistical properties.

317 Ensemble of Clustered Desparsified Lasso (EnCluDL) is a multivariate statistical
 318 inference procedure designed for spatial data; it was first introduced by [Chevalier et al.](#)
 319 [\[2018\]](#). EnCluDL relies on three steps: a spatially-constrained clustering algorithm for
 320 reducing the problem dimension, a statistical inference procedure for deriving statistical
 321 maps, and an ensembling method for aggregating the statistical maps.

322 **Statistical inference with Desparsified Lasso.** Desparsified Lasso (DL) is a statisti-
323 cal inference procedure that can be viewed as a generalization of the least-squares-based
324 inference in high dimension under sparsity assumptions. It was proposed and thoroughly
325 analyzed by Zhang and Zhang [2014] and van de Geer et al. [2014]. This estimator pro-
326 duces p-values on linear model parameters even when the number of parameters p is
327 (reasonably) greater than the number of samples n . A technical description of Desparsi-
328 fied Lasso is available in Sec. 7.1. In the neuroimaging context, the initial parameters are
329 related to the voxels, which are of the order of one hundred thousand while the number
330 of samples is almost always lower than one thousand. In such settings Desparsified Lasso
331 is inefficient due to a lack of statistical power, hence dimension reduction is required.

332 **Clustering.** As argued in Section 1, while performing dimension reduction, we aim at
333 keeping the spatial structure of the data and avoid mixing voxels "far" from each other.
334 This is achieved with data-driven parcellation along with a spatially constrained clus-
335 tering algorithm following the conclusions by Varoquaux et al. [2012] and Thirion et al.
336 [2014]. Another interesting aspect of this dimension reduction method is its denoising
337 property [Hoyos-Idrobo et al., 2018] since it produces averages from groups of noisy vox-
338 els. Note that this choice ultimately calls for a spatial tolerance on the statistical control,
339 *i.e.*, considering the δ -FWER instead of the standard FWER. Through the clustering,
340 the p voxels are grouped into C clusters, where $C \ll p$. Then, Desparsified Lasso is
341 directly applied to the compressed problem in order to produce corrected p-values. No-
342 tably, corrected p-values are obtained from the initial p-values by applying Bonferroni
343 correction [Dunn, 1961] with a factor $C \ll p$. Following the terminology in [Chevalier
344 et al., 2018], we refer to this procedure as Clustered Desparsified Lasso (CluDL). CluDL
345 however suffers from high variance [Chevalier et al., 2018] as it depends on an arbitrary
346 grouping choice. This can be alleviated by ensembling techniques, as described next.

347 **Ensembling.** Varoquaux et al. [2012], Hoyos-Idrobo et al. [2018] have shown that
348 randomizing the grouping choice and adding an ensembling step to aggregate several
349 solutions can stabilize the overall procedure. Additionally, Chevalier et al. [2018] have
350 highlighted that the ensembling step is also beneficial in terms of support recovery. To
351 perform B groupings of the covariates, we train the parcellations algorithm with B
352 different random subsamples of the original data sample. Then, thanks to the CluDL
353 procedure, we obtain B statistical maps that are aggregated into one through an en-
354 sembling procedure. The ensembling procedure we considered in the statistical inference
355 procedure is adapted from Meinshausen et al. [2009] that is described in appendix in
356 Sec. 7.2. We refer to the full inference algorithm as Ensemble of Clustered Desparsified
357 Lasso (EnCluDL). Under hypothesis ensuring Desparsified Lasso statistical properties
358 —notably sparsity and smoothness of the true weight map and i.i.d. data samples—
359 EnCluDL gives statistical guarantees, namely it controls the δ -FWER.

360 **Choosing δ for δ -FWER control** Theoretically, the minimal spatial tolerance δ
361 that guarantees a control of the δ -FWER with EnCluDL is the largest parcel diameter.

362 However, in practice, we aggregate many statistical maps obtained from different choices
 363 of voxel grouping; then the required spatial tolerance is reduced to the average radius.
 364 Then, the value of δ for which we observe the δ -FWER control varies approximately
 365 linearly with the cubic root of the average number of voxels per cluster. In standard
 366 fMRI settings, we propose the following formula for δ :

$$\delta_0 = \left(\frac{p}{2C} \right)^{1/3}, \quad (12)$$

367 the ratio p/C being the average number of voxels per cluster, δ_0 is a distance in voxel
 368 size unit.

369 Note that the previous formula is an estimate of the average cluster radius that
 370 assumes that the shape of the clusters have identical cubic shape. In practice, this
 371 formula tends to underestimate the average cluster radius but was suitable in all our
 372 experiments. In [Sec. 7.6](#), we study empirically the distribution of the cluster radius
 373 distribution as a function of the number of clusters, and compare it with δ_0 .

374 Additionally, note that when the setting is particularly favorable for inference, *e.g.*, if
 375 $\log(n)/C$ is large, the choice of δ given by (12) might be slightly too liberal. To address
 376 these specific cases, we propose a more refined formula to estimate δ in appendix in
 377 [Sec. 7.5](#).

378 **EnCluDL hyper parameters.** The number of clusters C is a crucial hyperparameter
 379 of EnCluDL. Generally, a suitable C depends on intrinsic physical properties of the
 380 problem and on the targeted spatial tolerance δ . Decreasing C increases the statistical
 381 power while reducing the spatial precision. In the neuroimaging context, taking $C =$
 382 500 is a fair default value achieving a suitable trade-off between spatial precision and
 383 statistical power when the number of samples is a few hundreds. With this choice, the
 384 spatial tolerance should be close to $\delta = 10$ mm when working with masked fMRI data.

385 As a more adaptive approach, we recommend tuning C according to n *e.g.*, $C \in$
 386 $[n/2, n]$. This choice should still ensure the δ -FWER control with δ given by (12) (or its
 387 corrected version, see appendix [Sec. 7.5](#)) and is justified in [Sec. 4.5](#).

388 The parameter B , the number of CluDL solutions to be aggregated, is discussed in
 389 [Sec. 3.5](#). The larger B the more stable the solution, yet the heavier the computational
 390 cost. In our experiments, we have set $B = 25$ (see [Hoyos-Idrobo et al. \[2018\]](#) for a more
 391 complete discussion on this parameter).

392 **Empirical analysis of data structure assumptions for EnCluDL.** The core part
 393 of EnCluDL consists in applying Desparsified Lasso to a clustered version of the original
 394 problem. As disclaimed in [van de Geer et al. \[2014\]](#), some technical hypotheses on the
 395 structure of the design matrix \mathbf{X} —*i.e.*, of the reduced data— are necessary to produce
 396 valid confidence intervals on the parameters with Desparsified Lasso. Roughly, it is
 397 necessary that the features are "not too much correlated". In appendix in [Sec. 7.3](#), we
 398 show in a simple setting that as long as the correlation between two predictive features

399 is less than 0.8, it is possible to recover both features. However when the correlation
400 between features is more than 0.9, only one of the two features can be identified.

401 In [Sec. 7.4](#), we show that in standard fMRI datasets neighboring voxels can have
402 a correlation greater than 0.9. Thus applying Desparsified Lasso at the voxel level
403 certainly leads to many false negatives. However, since Desparsified Lasso is applied
404 to the clustered problem, we have to consider correlation between clusters instead. In
405 [Sec. 7.4](#), we show on HCP data that such inter-cluster correlation is almost always
406 lower than 0.8 and always lower than 0.85. This means that data structure assumptions
407 for EnCluDL are sustainable. Additionally, the fact that EnCluDL aggregates several
408 CluDL solutions increases the tolerance to inter-cluster correlation.

409 3.6 A complementary univariate solution

410 Given the complementarity of univariate and multivariate inference noted previously, we
411 add to our study a univariate inference method, namely *univariate permuted OLS* (Univ-
412 OLS). This method does not test the same null hypothesis as the other methods: it tests
413 whether or not a voxel is marginally associated with the target. Then, while it should
414 not be benchmarked with the other methods, we propose to consider jointly the results
415 obtained by the marginal and the conditional analyses, as advocated by [Weichwald et al.](#)
416 [\[2015\]](#).

417 The Univ-OLS method is based on the generalized linear model (GLM) [[Friston et al.](#),
418 [1994](#)]. For every voxel we compute a t-statistic by applying the OLS procedure on the
419 linear model that associates each voxel with the target. Subsequently, we also derive the
420 permuted t-statistic distribution by performing the OLS on permuted data. Finally, to
421 obtain corrected p-values, we use the standard maxT procedure [[Westfall and Young](#),
422 [1993](#)]. Note that, for this method, we have used the `permuted_ols` function implemented
423 in the Nilearn python package [[Abraham et al., 2014](#)] with 1000 permutations.

424 3.7 Implementation

425 The Python code that implements Thr-SVR, Perm-SVR, Ada-SVR and EnCluDL can be
426 found on <https://github.com/ja-che/hidimstat>. Our algorithms are implemented
427 with Python = 3.6.8 and need the following packages Numpy = 1.16.2 [[Van der Walt](#)
428 [et al., 2011](#)], Scipy = 1.2.1 [[Virtanen et al., 2020](#)], Scikit-Learn = 0.21 [[Pedregosa et al.](#),
429 [2011](#)], Joblib = 0.11 and Nilearn = 0.6.0 [[Abraham et al., 2014](#)].

430 4 Experimental procedures

431 4.1 Data

432 To validate empirically the statistical guarantees of the four algorithms —Thr-SVR,
433 Perm-SVR, Ada-SVR and EnCluDL— described in [Section 3](#), we perform several ex-
434 periments on resting-state fMRI and task fMRI data. We also show some results for
435 Univ-OLS to highlight the complementarity of univariate and multivariate analyses, in

436 particular when studying predictive patterns on real data. We focus on three datasets:
437 HCP900 resting-state fMRI, HCP900 task fMRI and RSVP task fMRI.

438 **HCP900 resting-state fMRI data.** HCP900 resting-state fMRI dataset [Van Essen
439 et al., 2012] contains 4 runs of 15 minutes resting-state recordings with a 0.76s-repetition
440 time (corresponding to 1200 frames per run) for 796 subjects. We use the MNI-resampled
441 images provided in the HCP900 release. For this dataset the number of samples is equal
442 to 1200 (only one run is used) and the number of voxels is 156 374 after gray-matter
443 masking (the spatial resolution being 2 mm isotropic).

444 **HCP900 task fMRI data.** We also use the HCP900 task-evoked fMRI dataset [Van
445 Essen et al., 2012], in which we take the masked 2 mm z-maps of the 796 subjects
446 from 6 tasks to solve 7 binary classification problems: emotion (*emotional face vs shape*
447 *outline*), gambling (*reward vs loss*), language (*story vs math*), motor hand (*left vs right*
448 *hand*), motor foot (*left vs right foot*), relational (*relational vs match*) and social (*mental*
449 *interaction vs random interaction*). We consider the fixed-effect maps for each outcome
450 (or condition), yielding one image per subject per condition (which corresponds to two
451 images per subject for each classification problem). Then, for each problem, the number
452 of samples available is 1592 ($= 2 \times 796$) and the number of voxels is 156 374 after
453 gray-matter masking.

454 **Unmasked RSVP task fMRI data.** We also use activation maps obtained from
455 a rapid serial visual presentation (RSVP) task of the individual brain charting dataset
456 [Pinho et al., 2018], augmented with 9 additional subjects performing the same task,
457 under the same experimental procedures and scanning parameters. No masking is used
458 for this dataset, so that out-of-brain voxels are not withdrawn from preprocessing. We
459 consider the unmasked 3 mm-resolution statistical z-maps of the 6 sessions of the 21 sub-
460 jects for a reading task with 6 different contrasts that have been grouped into 2 classes:
461 language (words, simple sentences, complex sentences) vs pseudo-language (consonant
462 strings, pseudo-word lists, jabberwocky). The images are all registered to MNI space and
463 per-condition effects are estimated with Nistats v0.0.1 library [Abraham et al., 2014].
464 For this dataset the number of samples available is equal to 756 (21 subjects \times 6 runs \times 6
465 images per run) and the number of voxels is 173 628 (unmasked images resampled at
466 3-mm resolution). We run the inter-subject experiment described in Sec. 4.4 with this
467 dataset.

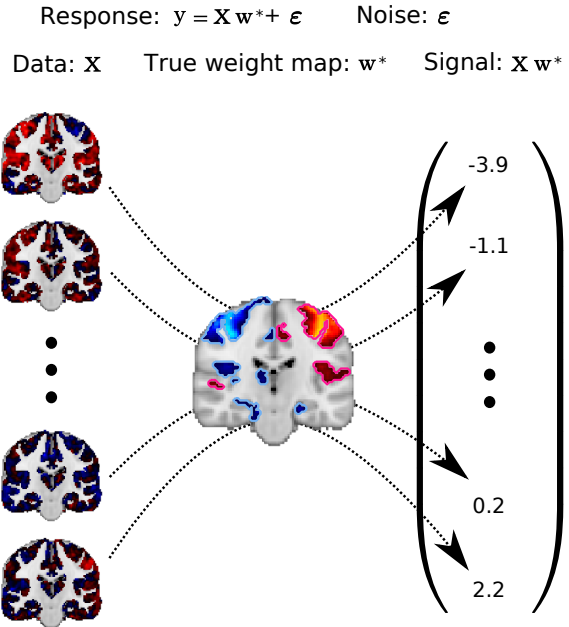
468 4.2 Statistical control on semi-simulated data

469 A first series of experiments study whether the four different methods exhibit the ex-
470 pected δ -FWER control and are competitive in terms of support recovery, as measured
471 with the precision-recall curve. To do so, we have to construct the true weight map \mathbf{w}^* .
472 We generate “semi-simulated” data: generating signals from estimates on real data. To

473 avoid circularity in the definition of the ground truth, we used two different tasks: one
 474 to build \mathbf{w}^* and another one to define \mathbf{X} .

475 **Building a reference weight map from HCP900 motor hand dataset.** To con-
 476 struct an underlying weight map, we use the motor hand (MH) task of the HCP900 task
 477 fMRI dataset described in Sec. 4.1. Specifically, we build a design matrix $\mathbf{X}_{\text{MH}} \in \mathbb{R}^{n \times p}$
 478 from the motor hand task z-maps of all subjects associated with a binary target index
 479 \mathbf{y}_{MH} . To obtain an initial weight map $\mathbf{w}_{\text{MH}}^{\text{SVC}}$ we regress \mathbf{X}_{MH} against \mathbf{y}_{MH} by fitting
 480 a linear Support Vector Classifier (SVC) [Cortes and Vapnik, 1995]. From $\mathbf{w}_{\text{MH}}^{\text{SVC}}$
 481 only kept the 10% most extreme values ensuring that the connected groups of non zero-
 482 weight voxels have a minimal size of 1 cm^3 by removing small clusters. We chose this
 483 map (represented in Fig. 3 and Fig. 4) to be the true weight map $\mathbf{w}^* \in \mathbb{R}^p$ for the whole
 484 simulated experiments.

Figure 3: **Generating a hybrid dataset with known ground truth and actual fMRI data.** To generate the response for a given sample we multiply the corresponding brain activation map by the true weight map and add a Gaussian noise with fixed variance. To highlight the predictive regions, we circle them in pink for positive coefficients and in light blue for negative coefficients. As an illustration, we take four different data samples with negative or positive output value.



485 **Simulating responses with HCP900 emotion dataset.** We then take \mathbf{X} to be
 486 the set of z-maps from the emotion task of the HCP900 task fMRI dataset described in
 487 Sec. 4.1. To generate a continuous response vector \mathbf{y} , we draw a Gaussian random noise
 488 vector $\epsilon \sim \mathcal{N}(\mathbf{0}, \sigma_\epsilon^2 \mathbf{I}_n)$ and use the linear model introduced in (1), where $\sigma_\epsilon = 0.2$ to
 489 reach $\text{SNR}_y = 10$, where SNR_y is given by:

$$\text{SNR}_y = \frac{\|\mathbf{X} \mathbf{w}^*\|^2}{n \sigma_\epsilon^2} . \quad (13)$$

490 The way we simulate \mathbf{y} is summarized in Fig. 3.

491 **Quantification of error control and detection accuracy.** To obtain representa-
492 tive results, we then run the procedures described in [Section 3](#) for 100 different response
493 vectors \mathbf{y} generated from different random samples of subjects and different draws of ε .
494 We let the number of samples vary from $n = 50$ (25 random subjects taken among the
495 796) to $n = 1200$ (600 subjects), the number of voxels being $p = 156\,374$. For each sim-
496 ulation, we record the empirical δ -FWER and the precision-recall curves. Importantly,
497 we do not recommend running such analysis with $n < 100$, since the estimation problem
498 is hard and statistical guarantees are only asymptotic.

499 **Heavy-tailed version of the semi-simulated experiment.** In the above experi-
500 ment the noise is Gaussian, hence we also benchmark the inference procedures for Laplace
501 and Student noise to assess the impact of noise distribution.

502 **Binary version of the semi-simulated experiment.** In the main experiment the
503 response vector \mathbf{y} is continuous, hence we also benchmark the inference procedures for a
504 binary response. For that, we simply take as response vector the signs of the continuous
505 \mathbf{y} generated as in the previous paragraph.

506 **Univ-OLS solves another inference problem.** Univariate methods do not compete
507 with multivariate methods, as they do not test the same null hypotheses. However, for
508 pedagogical purpose, we show that Univ-OLS based FWER control is not valid in the
509 multivariate analysis setup.

510 4.3 Statistical control under the global null with i.i.d. data

511 In this experiment, we test whether the procedures control the FWER under a global
512 null model. EnCluDL only controls the δ -FWER theoretically but, when the true weight
513 vector \mathbf{w}^* is null, the δ -FWER and the classical FWER are identical. Then, all pro-
514 cedures should control the FWER. Here, we considered the tasks of the HCP900 task
515 fMRI dataset described in [Sec. 4.1](#) keeping all the subjects ($n = 1592$). Then, to get
516 a noise-only response, we (uniformly) randomly permute the original response vector.
517 Similarly as in [Sec. 4.2](#), the i.i.d. hypothesis is legitimate, since the data correspond to
518 z-maps of different subjects. For each task, we draw 100 different permutations of the
519 response and check if the different methods enforce the chosen nominal FWER of 10%.

520 to illustrate the importance of checking the underlying assumptions, in appendix in
521 [Sec. 7.8](#), we describe an additional experiment to show that FWER (or δ -FWER) is not
522 controlled anymore when working with an autocorrelated response vector, breaking the
523 i.i.d hypothesis. This experiment is adapted from [Eklund et al. \[2016\]](#).

524 4.4 Statistical control of out-of-brain detections

525 In this experiment we test the four procedures on an unmasked task fMRI dataset to
526 verify that no spurious detection is made outside of the brain —up to the allowed error
527 rate. Indeed, the non-null coefficients of the weight vector \mathbf{w}^* should all be contained

528 in the brain since there is no informative signal in out-of-brain voxels. To do so, we
529 take the unmasked RSVP task fMRI dataset, described in [Sec. 4.1](#) (with design matrix
530 \mathbf{X} containing $n = 756$ unmasked z-maps). Then, we report how frequently some voxels
531 are detected outside the brain volume. For the sake of completeness, we also check the
532 non-occurrence of out-of-brain detections with Univ-OLS.

533 **4.5 Insights on the choice of number of clusters**

534 In this experiment, we assess empirically the impact of C , the number of clusters used in
535 the EnCluDL algorithm. We use the same generative method as in [Sec. 4.2](#) to produce
536 an experiment with known ground truth. Then, we run the EnCluDL algorithm varying
537 the numbers of clusters C from $C = 200$ to $C = 1000$. We also vary the number of
538 samples n from 100 to 1200. As in [Sec. 4.2](#), we run the experiment for 100 different
539 response vectors and report aggregated results. We report two statistics: the empirical
540 δ -FWER and the AUC of the precision-recall curve for every value of C and n .

541 **4.6 Face validity on HCP dataset**

542 In this experiment, we consider the output of the procedures in terms of brain regions
543 that are conditionally associated with the task performed by the subjects. Similarly as
544 in [Sec. 4.3](#), we consider the tasks of the HCP900 task fMRI dataset described in [Sec. 4.1](#),
545 keeping this time the true response vector. We run all the procedures on every task and
546 report the statistical maps thresholded such that the FWER $< 10\%$ or the δ -FWER $<$
547 10% (for EnCluDL). For this, we use all the available samples ($n = 1592$). We also
548 include Univ-OLS to compare the discriminative patterns obtained with a univariate
549 inference.

550 **4.7 Prediction performance**

551 Even if it is not the purpose of this study, we also checked the prediction performance of
552 the decoders produced by each method. Since Thr-SVR and Perm-SVR rely on the same
553 predictive function, there are three different decoders: SVR, Ada-SVR and EnCluDL.
554 To perform this experiment, we consider the tasks of the HCP900 task fMRI dataset
555 described in [Sec. 4.1](#). We run all the procedures on every task using a sample size
556 $n = 400$, keeping the rest of the samples to test the trained model. For each task and
557 each method, we take 100 different random subsamples to produce the results. This
558 experiment being a side study, we give the results in appendix in [Sec. 7.12](#).

559 **5 Results**

560 In this section, after setting the value of the tolerance parameter δ in the different
561 datasets, we present the experimental results.

5.1 Estimating δ in HCP and RSVP datasets

In all the experiments, unless specified otherwise, we run EnCluDL with the default choice $C = 500$. Reversing (12), we obtain a tolerance parameter of $\delta_{\text{HCP}} = 5.4$ voxels for HCP900 and $\delta_{\text{RSVP}} = 5.6$ voxels for RSVP, corresponding to $\delta_{\text{HCP}} = 12$ mm and $\delta_{\text{RSVP}} = 18$ mm respectively after rounding up. In Fig. 14 in appendix, we display the spatial tolerance of 6 voxels in the case of HCP data.

5.2 Statistical control with known ground truth

Here, we describe the results obtained from the experiment described in Sec. 4.2.

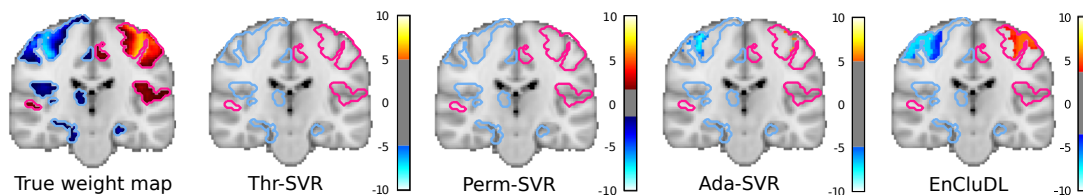


Figure 4: **Qualitative comparison of the model solutions.** Here, we show the solutions (z-maps) given by the four inference procedures, for a single random draw of the noise vector in the experiment described in Sec. 4.2. The weight maps are thresholded such that δ -FWER $< 10\%$ theoretically. We can observe that none of the methods yield false discoveries but the Ensemble of Clustered Desparsified Lasso (EnCluDL) procedure is the most powerful followed by Adaptive Permutation Threshold SVR (Ada-SVR).

Qualitative comparison of the model solutions. In Fig. 4, we present a qualitative comparison of the model solutions when $n = 400$. None of the methods yields false discoveries for the chosen threshold—taken such that δ -FWER $< 10\%$. EnCluDL recovers more active regions than the other procedures, which makes it the most powerful procedure, followed by Ada-SVR. The other two procedures do not discover the expected patterns. These results displayed are obtained for a single random draw of the noise vector, but similar results holds for different draws.

δ -FWER control. In this experiment, we check if Thr-SVR, Perm-SVR, Ada-SVR and EnCluDL control the δ -FWER at the targeted nominal level (here being 10%). Fig. 5 shows that Perm-SVR and EnCluDL procedures control the δ -FWER for all sample sizes since their empirical δ -FWER remain below the targeted nominal level, whereas Thr-SVR and Ada-SVR fail to control the δ -FWER in every setting. In particular, the empirical δ -FWER for Ada-SVR is above the targeted nominal level for $n \geq 800$. This might occur since the approximation made by (9) is valid only if n remains “sufficiently low” [Gaonkar and Davatzikos, 2012]. Thr-SVR fails to control empirically the δ -FWER for any value of n . This might be due to the two assumptions made in Sec. 3.2 not being satisfied—it is indeed unlikely that the SVR weights of the null region follow the same

587 distribution. We further discuss this point in [Section 6](#). Concerning EnCluDL, one can
 588 notice that the empirical δ -FWER is slightly larger for $n = 1200$, this effect is explained
 589 in appendix in [Sec. 7.5](#) and [Sec. 7.6](#). We report additional results, notably heavy-tailed
 590 and binary version of the experiment, in appendix in [Sec. 7.10](#). These lead to the same
 591 statistical behavior as observed here.

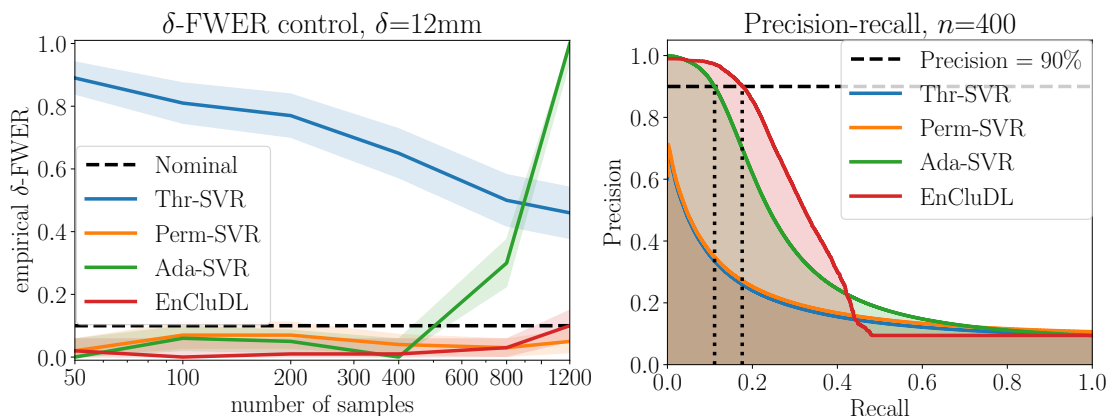


Figure 5: δ -FWER control and precision-recall curve on semi-simulated data (known ground truth). Left: The results of the experiment described in [Sec. 4.2](#) show that the permutation test (Perm-SVR) and Ensemble of Clustered Desparsified Lasso (EnCluDL) are the only procedures that correctly control the δ -FWER at the nominal level (10%). This is not the case for Adaptive Permutation Threshold SVR (Ada-SVR) and Thresholded SVR (Thr-SVR) procedures. Right: For the same experiment, EnCluDL has the best performance in terms of precision-recall curve. For $n = 400$, and ensuring 90% precision, EnCluDL obtains a recall of 23% and Ada-SVR a recall of 16%. Thr-SVR and Perm-SVR share the same precision-recall curve and were not able to reach 90% precision.

592 **Precision-recall.** In this experiment, we also evaluate the recovery properties of the
 593 four methods by comparing the precision-recall curve for different value of n . [Fig. 5](#)
 594 shows that EnCluDL has the best precision-recall curve for $n = 400$. We recall that
 595 the perfect precision-recall curve is reached if the precision is equal to 1 for any value
 596 of recall between 0 and 1. Similar results were obtained for the other sample sizes
 597 tested (appendix [Fig. 17](#)). Indeed, when $n = 400$, for a 90% precision, EnCluDL gives
 598 a recall of 23% and Ada-SVR a recall of 16%. Thr-SVR and Perm-SVR share the same
 599 precision-recall curve since they both produce p-values arranged in the reverse order of
 600 the absolute SVR weights. These thresholding methods were not able to reach the 90%
 601 precision; their recovery properties are much weaker.

602 We report additional results in [Sec. 7.10](#).

603 5.3 Statistical control under the global null with i.i.d. data

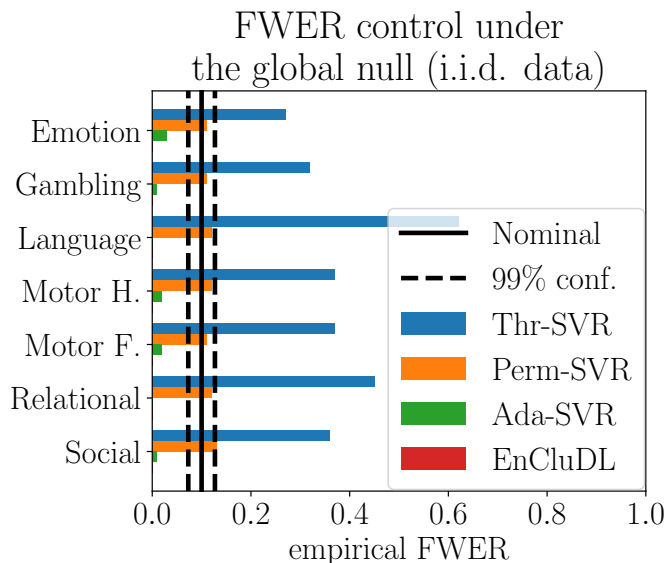
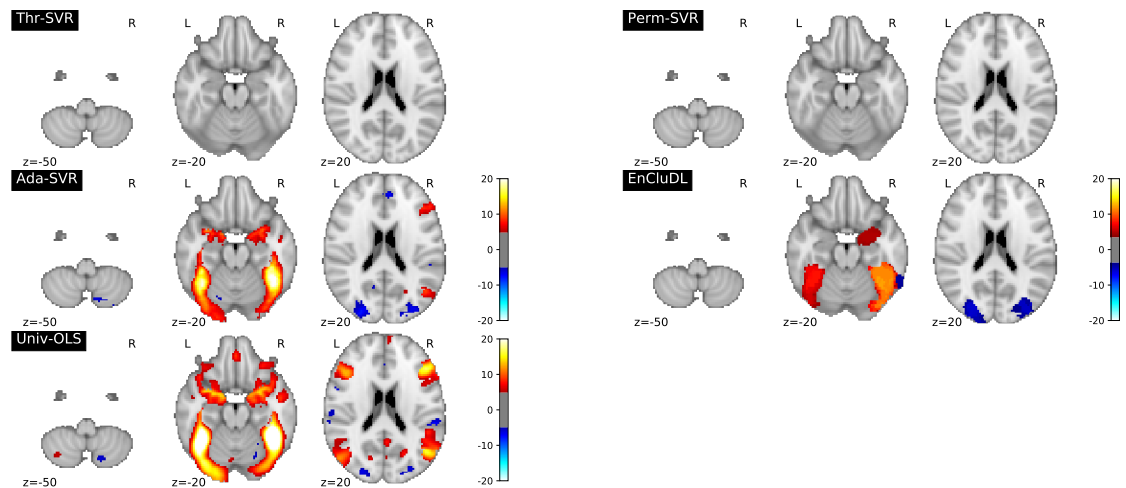


Figure 6: **FWER control under the global null with i.i.d. data** The results of the experiment with i.i.d. data under the global null, described in [Sec. 4.3](#), show that, only the Thresholded SVR (Thr-SVR) fails to control the FWER empirically in this context. EnCluDL makes no detection: it is a conservative approach, as one could expect from theory.

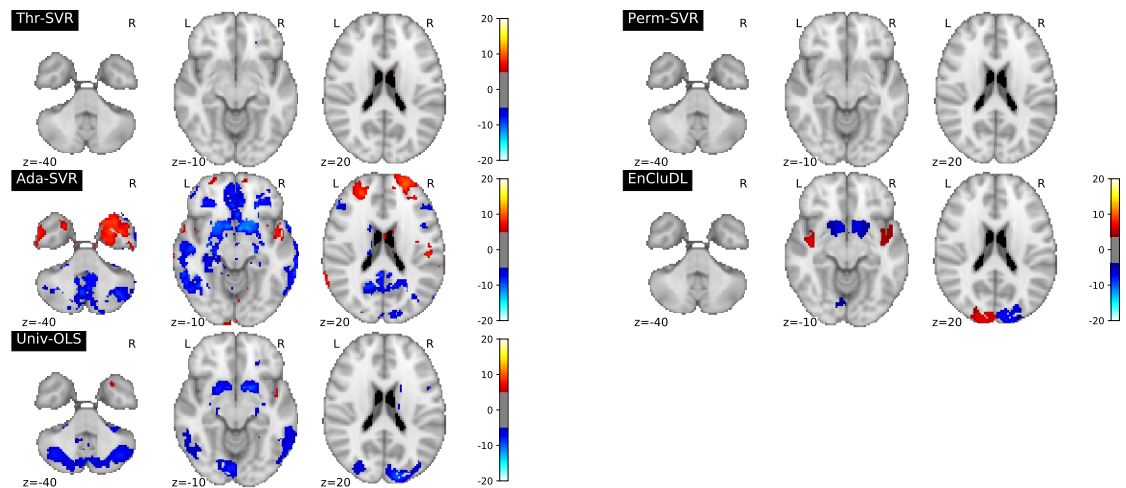
604 **FWER control under the global null (permuted response).** Here, we summa-
 605 rize the results of the experiment testing control of the FWER in a global null setting
 606 ([Sec. 4.3](#)). [Fig. 6](#) shows that, when samples are i.i.d., all the procedures control the
 607 FWER, except Thr-SVR. EnCluDL is even conservative since the empirical FWER re-
 608 mains at 0 for all the different tasks tested. This result is not surprising since at least
 609 two steps of the EnCluDL procedure are conservative: the Bonferroni correction and the
 610 ensembling of the p-values maps.

611 **Face validity (original response).** Additionally, we run the procedures with the
 612 original (not permuted) response vector to check whether the methods can recover pre-
 613 dictive patterns; this corresponds to the experiment described [Sec. 4.6](#). We plot the
 614 results for the two first tasks (emotion and gambling) in [Fig. 7](#); see appendix [Fig. 23](#)
 615 for the five other tasks. Qualitatively, EnCluDL recovers the most plausible predictive
 616 patterns, Ada-SVR sometimes makes dubious discoveries: patterns are too wide and
 617 implausible. The two other methods exhibit a very weak statistical power.

618 Comparing EnCluDL and Univ-OLS solutions, we see that the discovered patterns
 619 are not a subset of each other. This result was expected given the arguments in [Weich-](#)
 620 [wald et al. \[2015\]](#): the advantage of combining the two paradigms is to get more insight
 621 on the causal nature of the relation between the voxel signals and the target.



(a) Emotion



(b) Gambling

Figure 7: **Estimated predictive patterns on standard task fMRI dataset.** Here, we plot the results for the emotion and gambling tasks of the experiment described in [Sec. 4.6](#) thresholding the statistical maps such that the δ -FWER stays lower than 10% for $\delta = 12$ mm. Qualitatively, EnCluDL discovers the most plausible patterns, Ada-SVR sometimes makes dubious discoveries, patterns are too wide and implausible, while the two other methods exhibit a very weak statistical power. Univariate analysis results obtain with Univ-OLS clearly provide distinct information about the relationship between the voxel signals and the outcome. The results of the five other tasks are available in [Fig. 23](#).

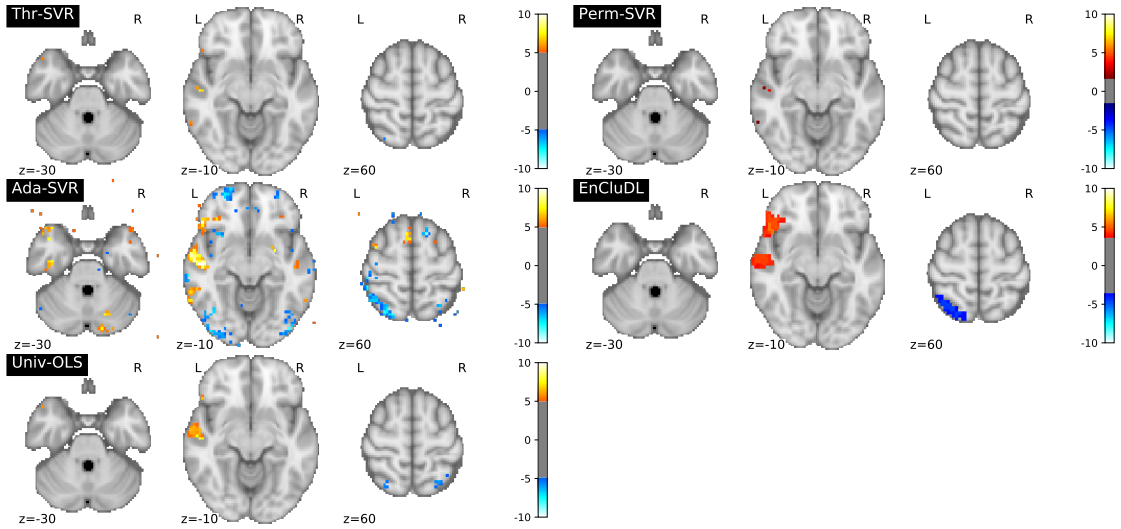


Figure 8: **Statistical maps for unmasked RVSP data.** The results of the unmasked task-fMRI experiment, described in Sec. 4.4, show that EnCluDL, Thresholded SVR (Thr-SVR) and the permutation test (Perm-SVR) do not return out-of-brain discoveries, while the Adaptive Permutation Threshold SVR (Ada-SVR) does. Here z-score maps are thresholded such that the δ -FWER is at most 10% for $\delta = 6$ voxels (or 18 mm). Thr-SVR and the Perm-SVR do not yield spurious detections but very few detections are made, hence these methods have low statistical power. EnCluDL does not make any spurious detection; rather it makes detections in the temporal lobe and Broca’s area, which are expected for a reading task. Univ-OLS does not make any out-of-brain detection either but returns significant associations in the temporal lobe.

622 5.4 Statistical control of out-of-brain discoveries

623 We now report the results from the unmasked RSVP task data experiment (Sec. 4.4).
 624 Here, we check whether out-of-brain detections are made. In Fig. 8, the z-score maps
 625 are thresholded such that the FWER (for Perm-SVR, Thr-SVR, and Ada-SVR) or the
 626 δ -FWER (for EnCluDL) are at most 10% for $\delta = 6$ voxels (or 18 mm). We observe
 627 that Ada-SVR makes some out-of-brain discoveries, and it does not control the FWER
 628 empirically. Thr-SVR and Perm-SVR do not yield spurious detections but very few
 629 detections are made, hence these methods have low statistical power. EnCluDL does
 630 not make any out-of-brain detections and it outlines predictive regions in the temporal
 631 lobe and Broca’s area, expected for a reading task. Finally, Univ-OLS does not make
 632 any spurious detection either; it only makes detections in the temporal lobe.

633 5.5 Insights on choosing the number of clusters

634 Here, we report the results obtained of the experiment task-fMRI data (Sec. 4.5) study-
 635 ing the impact of C (number of clusters) on the δ -FWER control and the recovery

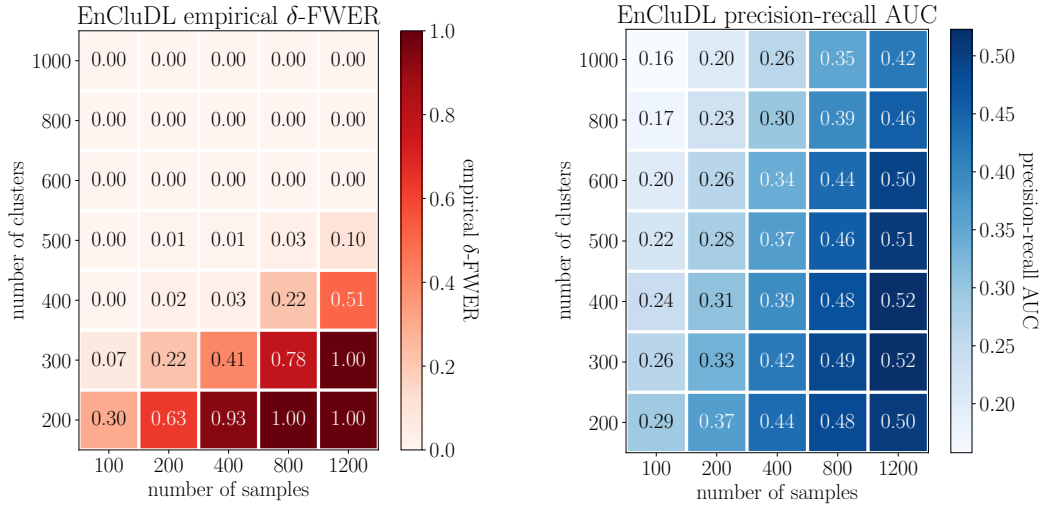


Figure 9: **Influence of the number C of clusters on δ -FWER control and the recovery properties of EnCluDL.** The results of the experiment described in Sec. 4.5 show the impact of C on the δ -FWER control and the recovery score of EnCluDL. When $C \geq 500$, clusters are smaller, hence the δ -FWER is controlled for $\delta = 12$ mm (and potentially lower values of δ) since all the empirical δ -FWER's are lower than the 10% nominal rate. Conversely, when $C < 500$, clusters are wider and the spatial tolerance is overcome by the model inaccuracy, hence the δ -FWER is not controlled for $\delta = 12$ mm. However, it remains controlled for higher values of δ . Concerning the recovery properties we see that reducing the number of clusters improves the precision-recall curves. Thus, the more spatial uncertainty is tolerated, the best recovery properties EnCluDL offers.

636 properties of EnCluDL for various sample sizes. These results are obtained with 100
637 repetitions for every sample and cluster sizes. In Fig. 9, we notice that a lower C leads
638 to improved recovery, according to the area under the precision-recall curves, for $\delta = 6$
639 voxels (or 12 mm). However, when the number of cluster is lower, the average cluster
640 radius increases and overcomes the spatial tolerance of δ , leading to inflated error rates
641 (cf. Sec. 7.6). More precisely, the δ -FWER is controlled when $C \geq 500$. Note that for
642 $C < 500$, it is possible to control the δ -FWER, even when n is small, provided a larger
643 spatial tolerance $\delta > 6$ voxels. To compute the requested δ , one can use (12). Besides,
644 we observe that the recovery score of EnCluDL improves when n increases, as expected.
645 We also notice that the empirical δ -FWER increases with n . To explain this effect, we
646 first recall that theoretically the δ -FWER is controlled for δ equal to the largest cluster
647 diameter, likely to be too large in practice. In this study, we have taken δ equal to δ_0 ,
648 which is slightly smaller than the average radius of the clusters (cf. Sec. 7.6), since in
649 practice this choice ensures the δ -FWER control. However, when the setting is particu-
650 larly favorable for inference (*e.g.*, if $\log(n)/C > 1.5 \times 10^{-2}$), some false discoveries can
651 be made at a distance greater than the average radius from the support. The choice of δ

652 is further discussed in [Sec. 3.5](#) and in appendix in [Sec. 7.5](#). Additionally, we can notice
653 from [Fig. 9](#) that for a fixed C/n ratio the recovery capability is stable (see also appendix
654 [Sec. 7.9](#)). Then, as discussed in [Sec. 3.5](#), we advise taking C of the same order as n
655 (e.g., $C \in [n/2, n]$) when the goal is to recover most of the predictive regions without
656 strict requirements on the accuracy of their shapes —since the value of δ given by [\(12\)](#)
657 might be not small with regards to the predictive region itself.

658 6 Discussion

659 Decoding models are fundamental for causal interpretation of the implication of brain
660 regions for an outcome of interest, mental process or disease status [[Weichwald et al.,](#)
661 [2015](#)]. They produce weight maps that are needed to support this type of inference
662 [[Poldrack, 2011, Varoquaux et al., 2018](#)]. These weight maps capture how brain regions
663 relate to the outcome, *conditional on* the other regions, which is a key difference with re-
664 spect to standard brain mapping based on mass univariate models. However, the weight
665 maps produced by the common decoders come without statistical guarantees. Indeed,
666 decoders optimize the quality of their prediction, but give no control on conditional
667 feature importance. This is difficult due to the large number of covariates —voxels—
668 as well as the severe multi-collinearity: voxel-level inference is untenable. On the other
669 hand, given the spatial structure of the data, a spatial tolerance in the statistical control
670 is natural, as in Gaussian random field theory used in standard analysis [[Nichols, 2012](#)].

671 Our first contribution is to formalize this spatial statistical control by introducing
672 the δ -FWER, a control of false discoveries up to a spatial slack δ . This definition uncov-
673 ers a fundamental trade-off between accuracy in the localization of the brain structures
674 involved and statistical power: here we deliberately degrade spatial accuracy, acknowl-
675 edging current concerns on statistical power in neuroimaging studies [[Button et al., 2013,](#)
676 [Noble et al., 2019](#)].

677 Our second contribution is to study empirically the statistical control of four pro-
678 cedures computing decoding maps, ranging from thresholding procedures applied to
679 SVR weights, to a dedicated decoding procedure, EnCluDL. Experiments show that the
680 Thr-SVR procedure, thresholding SVR weights, fails to achieve useful statistical con-
681 trol. Exact permutation testing yields the expected statistical control but with very
682 poor statistical power for all experimental settings we have studied. On the other hand,
683 Adaptive Permutation Threshold SVR (Ada-SVR) [[Gaonkar and Davatzikos, 2012](#)], does
684 not control the FWER as it should, though it exhibits a fair precision-recall curve in
685 our semi-simulated experiments. This shows how difficult it is to identify a statistically
686 valid threshold for SVR weight maps. This is due to the fact that under the null hypoth-
687 esis, estimated weights are not distributed according to a fixed distribution —notably
688 because of the dependency structure of the data— and more precisely, the variance of
689 these distributions differs. Then, thresholding linear decoders (SVR, logistic regression)
690 based on their estimated weights amplitudes is not a principled approach to control false
691 discoveries.

692 EnCluDL uses a different decoding procedure to estimate the weight maps [[Chevalier](#)

693 et al., 2018], and as a result comes with theoretical statistical guarantees: it controls
694 the δ -FWER for a predetermined tolerance parameter δ equal to the largest diameter
695 of the clusters, assuming that the observed samples are i.i.d. and that the weight maps
696 are homogeneous and sparse. The experiments show that, indeed, for i.i.d. scenarios,
697 EnCluDL controls the δ -FWER for δ equal to the average radius of the clusters. Though,
698 in some very high SNR or high sample size regimes, it might be necessary to take δ larger
699 than the average radius (see Sec. 7.5). In practice, our choice of δ is conservative, and
700 with current fMRI datasets, δ -FWER control holds for smaller δ , even in relatively large
701 cohorts ($n = 1200$).

702 In our experiments, the spatial tolerance is around 1cm. Given that the definition
703 of spatial location is blurred by inter-subject variability in group studies, this tolerance
704 does not seem problematic. The method can thus be used for inference in cognitive
705 neuroscience and population studies in psychiatry, neurology or epidemiology.

706 In addition, EnCluDL exhibits the best support recovery performance in the pro-
707 posed semi-simulated experiments with fMRI data but also finds patterns with good
708 face validity in more qualitative experiments plotted in Fig. 7. On the other hand, we
709 also notice that EnCluDL tends to be over-conservative. Taking into account the diffi-
710 culty of the problem and the fact that the convergence results are only asymptotic, we
711 do not recommend using EnCluDL with $n < 100$.

712 In the present study, we have considered that the confounding variable effects have
713 been removed during fMRI data preprocessing. However, it is still possible to include an
714 additional confounding variable to the covariates before performing the inference. With
715 regards to EnCluDL, we note that confounding variables should be handled separately
716 from the clustered brain features.

717 Although it is not the main purpose of this study, we also checked the prediction
718 performance of the decoders produced by each method. It is important to note that
719 EnCluDL has been designed for the recovery of conditional statistical associations, not
720 for prediction. In practice, the prediction performance is almost the same for SVR and
721 Ada-SVR, and is slightly better than the one of EnCluDL (see Fig. 24). For prediction
722 purpose, we recommend using *Fast Regularized Ensembles of Models* (FReM) [Hoyos-
723 Idrobo et al., 2018], which is a stable and computationally efficient decoder with state-
724 of-the-art prediction performance.

725 For pedagogical purpose, we have also considered a dataset where cross-sample in-
726 dependence is violated due to serial correlation, reproducing an experiment of Eklund
727 et al. [2016]. The ensuing loss of statistical control underlines the importance of the
728 i.i.d. hypothesis. Hence, EnCluDL should not be used to make inference from intra-
729 subject dataset recorded over one session. With these warnings in mind, we think that
730 EnCluDL can be used safely in neuroimaging context. Our code, implemented with
731 Python 3, can be found on <https://github.com/ja-che/hidimstat> along with some
732 examples.

733 We have not considered the method proposed by Nguyen et al. [2019] based on the
734 Knockoff filters [Barber and Candès, 2015, Candès et al., 2018] that yet appear to be an
735 appealing procedure, as it can only control the FDR. In this study we have focused on

736 δ -FWER control, and hence defer the analysis of FDR-controlling procedures to future
737 work. Also, we have not benchmarked post-selection inference procedures [Lee et al.,
738 2016, Berk et al., 2013], as we found them challenging to run in high dimensional settings
739 and prone to numerical underflows.

740 Our empirical results clearly show that standard thresholding procedures, including
741 classical permutation tests, are not reliable to infer regions importance on decoder maps,
742 due to the high number of covariates. Since, in neuroimaging studies, these maps are
743 used to give evidence on the brain regions that supports an outcome, it is crucial to use
744 a procedure with statistical control on the brain maps. Our study shows that EnCluDL
745 provides such a control.

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756 **Ethics statement.** No experiments on living beings were performed for this study.
757 Hence, IRB approval was not necessary. The data that we used were acquired in original
758 studies that had received approval by the original institution’s IRB. All data were used
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962 7 Appendix

963 7.1 Desparsified Lasso

964 **Additional notation.** For a matrix \mathbf{X} , $\mathbf{X}_{i\cdot}$ refers to the i -th row and $\mathbf{X}_{\cdot j}$ to the j -th
965 column, $\mathbf{X}_{i,j}$ refers to the element (i, j) , and $\mathbf{X}^{(-j)}$ refers to the matrix \mathbf{X} without the
966 j -th column. \mathbf{X}^\dagger denotes the Moore-Penrose pseudo-inverse of \mathbf{X} .

967 **Small-dimension insight.** The Desparsified Lasso procedure, introduced by [Zhang](#)
968 [and Zhang \[2014\]](#) extends the Ordinary Least Squares (OLS) procedure to $n < p$ cases.
969 Let us first recall the standard OLS framework ($n > p$). Starting from model (1), let us
970 define $\mathbf{z}_j \in \mathbb{R}^n$ the residual of the OLS regression of $\mathbf{X}_{\cdot j}$ versus $\mathbf{X}^{(-j)}$ given by:

$$\mathbf{z}_j = \mathbf{X}_{\cdot j} - \mathbf{X}^{(-j)} \hat{\mathbf{w}}^{(-j)}, \quad (14)$$

971 where $\hat{\mathbf{w}}^{(-j)}$ refers to the estimator of the OLS regression of $\mathbf{X}_{\cdot j}$ versus $\mathbf{X}^{(-j)}$. In
972 particular, $\mathbf{z}_j^\top \mathbf{X}_{\cdot k} = 0$ for all $k \in [p] \setminus \{j\}$. In this setting, we also have the following
973 result:

974 **Proposition 7.1.** *If $n > p$ and $\text{rank}(\mathbf{X}) = p$, then, for all $j \in [p]$:*

$$\hat{\mathbf{w}}_j^{\text{OLS}} = \frac{\mathbf{z}_j^\top \mathbf{y}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot j}}, \quad (15)$$

975 where $\hat{\mathbf{w}}^{\text{OLS}}$ is the parameter vector estimates obtained from the OLS regression of \mathbf{y}
976 against \mathbf{X} .

977 **Desparsified Lasso.** In this setting, it is not possible to construct a non-zero vector
 978 family $\{\mathbf{z}_j, j \in [p]\}$ (*i.e.*, a family verifying $\mathbf{z}_j \neq \mathbf{0}$ for all $j \in [p]$), such that $\mathbf{z}_j^\top \mathbf{X}_{\cdot,k} = 0$
 979 for all $k \neq j$. The idea proposed by [Zhang and Zhang \[2014\]](#) is to construct a family
 980 $\{\mathbf{z}_j, j \in [p]\}$ which would play the same role as the residual of the OLS regression of $\mathbf{X}_{\cdot,j}$
 981 versus $\mathbf{X}^{(-j)}$ in (14) but relaxing (slightly) the constraint $\mathbf{z}_j^\top \mathbf{X}_{\cdot,k} = 0$. To do so, instead
 982 of computing $\{\mathbf{z}_j, j \in [p]\}$ by OLS regression, they proposed to take the residual of the
 983 Lasso regressions¹ of $\mathbf{X}_{\cdot,j}$ against $\mathbf{X}^{(-j)}$. Then, from (1), one can derive the following:

$$\frac{\mathbf{z}_j^\top \mathbf{y}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} = \mathbf{w}_j^* + \frac{\mathbf{z}_j^\top \boldsymbol{\varepsilon}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} + \sum_{k \neq j} \frac{\mathbf{z}_j^\top \mathbf{X}_{\cdot,k} \mathbf{w}_k^*}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} . \quad (16)$$

984 Noticing that the second term in (16) is a noise term and plugging in an initial estimator
 985 $\hat{\mathbf{w}}^{(\text{init})}$ of \mathbf{w}^* in the third term —a standard choice being the Lasso— they propose the
 986 following estimator:

$$\hat{\mathbf{w}}_j = \frac{\mathbf{z}_j^\top \mathbf{y}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} - \sum_{k \neq j} \frac{\mathbf{z}_j^\top \mathbf{X}_{\cdot,k} \hat{\mathbf{w}}_k^{(\text{init})}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} . \quad (17)$$

987 Here, one can notice that (17) generalizes (15) to $n < p$. Then, from (16) and (17) one
 988 can derive:

$$\sigma_\varepsilon^{-1}(\hat{\mathbf{w}}_j - \mathbf{w}_j^*) = \underbrace{\sigma_\varepsilon^{-1} \frac{\mathbf{z}_j^\top \boldsymbol{\varepsilon}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}}}_{\boldsymbol{\eta}_j} + \underbrace{\sigma_\varepsilon^{-1} \sum_{k \neq j} \frac{\mathbf{z}_j^\top \mathbf{X}_{\cdot,k}}{\mathbf{z}_j^\top \mathbf{X}_{\cdot,j}} (\mathbf{w}_k^* - \hat{\mathbf{w}}_k^{(\text{init})})}_{\boldsymbol{\mu}_j} . \quad (18)$$

989 This yields:

$$\sigma_\varepsilon^{-1}(\hat{\mathbf{w}} - \mathbf{w}^*) = \boldsymbol{\eta} + \boldsymbol{\mu}, \quad \boldsymbol{\eta} \sim \mathcal{N}_p(\mathbf{0}, \boldsymbol{\Omega}) , \quad (19)$$

990 where:

$$\boldsymbol{\Omega}_{jk} = \frac{\mathbf{z}_j^\top \mathbf{z}_k}{(\mathbf{z}_j^\top \mathbf{X}_{\cdot,j})(\mathbf{z}_k^\top \mathbf{X}_{\cdot,k})} . \quad (20)$$

991 Asymptotically and under some sparsity assumptions (one can refer to [[Dezeure et al.,](#)
 992 [2015](#)] for more details), one can neglect the last term $\boldsymbol{\mu}$ and obtain:

$$\sigma_\varepsilon^{-1}(\boldsymbol{\Omega}_{jj})^{-1/2}(\hat{\mathbf{w}}_j - \mathbf{w}_j^*) \sim \mathcal{N}(0, 1) . \quad (21)$$

993 From (21), one can compute the confidence intervals and p-values of the coefficients of
 994 the estimated weight map. Note that similar estimators have been derived in parallel in
 995 [Javanmard and Montanari \[2014\]](#).

¹From our analysis, taking λ_j , the regularization parameter used in the Lasso regression of $\mathbf{X}_{\cdot,j}$ against $\mathbf{X}^{(-j)}$, equal to $0.01 \times \max_{k \in [p] \setminus \{j\}} |\mathbf{X}_{\cdot,j}^\top \mathbf{X}_{\cdot,k}|/n$ is appropriate to compute \mathbf{z}_j . Empirically, it results in a more conservative solution than the one proposed by [Zhang and Zhang \[2014\]](#) but it avoids doing computationally expensive grid-search.

996 **7.2 Adaptive quantile aggregation of p-values**

For the j -th voxel, we have a vector $(p_j^{(b)})_{b \in [B]}$ of p-values, with one p-value computed for each of the B clusterings. Then, the final p-value of the j -th feature is given by the adaptive quantile aggregation, as proposed by Meinshausen et al. [2009]:

$$p_j = \min \left\{ (1 - \log(\gamma_{\min})) \inf_{\gamma \in (\gamma_{\min}, 1)} \left(\gamma\text{-quantile} \left\{ \frac{p_j^{(b)}}{\gamma}; b \in [B] \right\} \right), 1 \right\},$$

997 where we have taken $\gamma_{\min} = 0.20$ in our experiments. Taking a value of γ_{\min} not too
 998 small (*e.g.*, $\gamma_{\min} \geq 0.20$) ensures that the discovered sources have received small p-values
 999 many times (*e.g.*, at least for $B/5$ different choices of clustering).

1000 **7.3 Empirical analysis of data structure impact**

1001 In this section, we propose two simulations to gain more insight concerning the assump-
 1002 tions about data structure that are necessary for Desparsified Lasso and EnCluDL to
 1003 have power. More precisely, we investigate up to which level of correlation two corre-
 1004 lated predictive features (having non-zero weight) are both identified. Indeed, when two
 1005 predictive features are highly correlated, there is a risk that the inference procedure only
 1006 detects one of the two.

1007 The first simulation has modest data dimension, which corresponds to that of data
 1008 after clustering. We use it to analyze the behavior of Desparsified Lasso. The second
 1009 simulation has a 2D structure with larger data dimension, it introduces short- and long-
 1010 range correlation structure, it is used to study EnCluDL.

1011 **First simulation: approximating the clustered data setting.** In this simulation
 1012 we set $n = 100$ and $p = 500$. We construct the design matrix \mathbf{X} such that features are
 1013 normally distributed and the first two features have a correlation equal to parameter ρ ,
 1014 while all the other features are independent. The weight \mathbf{w}^* is such that $\mathbf{w}_j^* = 1$ for
 1015 $1 \leq j \leq 10$ and $\mathbf{w}_j^* = 0$ otherwise. We also set $\sigma_\varepsilon = 1$ giving approximately $\text{SNR}_y = 12$
 1016 close to the SNR estimated in real fMRI datasets.

1017 To check the ability of Desparsified Lasso to identify two correlated features, we
 1018 compare the smallest z-score of the first two first features (“correlated features”) with the
 1019 smallest z-score of the two following features (“control features”) for different value of $\rho \in$
 1020 $(0, 1)$. While the minimum z-score of the control features should not vary significantly
 1021 and corresponds to a control value, the minimum z-score of the two correlated features
 1022 should decrease towards 0 when ρ increases to 1. Also, we look at the z-score of a random
 1023 non-predictive feature (“random null feature”) to get insight about the z-score threshold
 1024 value to declare a feature significant.

1025 **First simulation results.** In Fig. 10, we give the results for the first simulation.
 1026 When the correlation of the two correlated features increases, their identification using
 1027 the Desparsified Lasso procedure becomes harder. In this experiment, we observe that

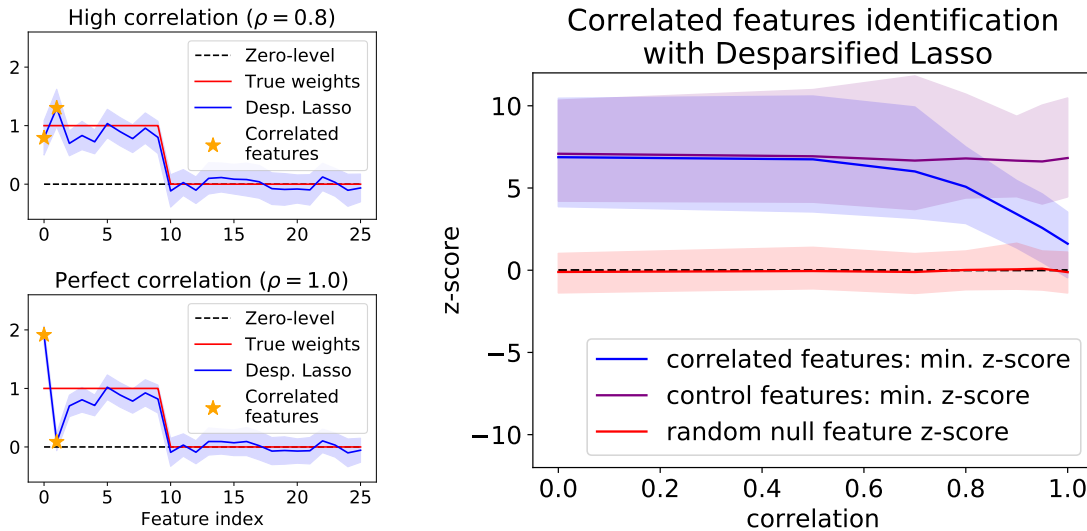


Figure 10: **Impact of correlation when trying to identify two correlated features.** Left: We plot the Desparsified Lasso estimator and its 95% confidence intervals. The correlation between the first two features is set to ρ , while the other features are uncorrelated. The higher ρ the harder it is to identify each of the two correlated features. For $\rho = 1.0$, it is impossible, while for $\rho = 0.8$, the identification of both features is successful. Right: Quantitative summary of the simulations. When the correlation increases the minimum z-score of the two first features (“correlated features”) decreases (90% confidence intervals also displayed). The correlation between the two following features (“control features”) remains equal to zero, thus the minimum z-score of these features is used as a control value that should not vary significantly. Also we plot the z-score of a random non-predictive feature (“random null feature”). We observe that for a correlation lower than 0.8 the deviation is limited and it is possible to identify the two correlated variables. For a correlation larger than 0.9 the deviation is massive and it becomes impossible to recover the two correlated variables.

1028 below a correlation of 0.8, Desparsified Lasso can identify accurately the two correlated
 1029 variables. However, above a correlation of 0.9, Desparsified Lasso might fail to recover
 1030 the both correlated variables.

1031 **Second simulation: 2D data structure.** The simulation we consider has a 2D data
 1032 structure. It aims at approximating the short- and long-range correlation structure that
 1033 can be observed in fMRI data (see [Sec. 7.4](#)). The feature space considered is a square
 1034 with edge length $H = 40$, then $p = H^2 = 1600$ features and we took $n = 100$ samples.
 1035 To construct \mathbf{w}^* , we define a 2D weight map $\tilde{\mathbf{w}}^*$ of size $H \times H$ with four active regions
 1036 then we flatten $\tilde{\mathbf{w}}^*$ in a vector \mathbf{w}^* of size p . Each active region is a small square of width
 1037 $h = 4$, leading to support of size $4 \times h^2 = 64$. The four active regions are located in the
 1038 corners of the weight map. The true weight map is represented in [Fig. 11](#). To construct

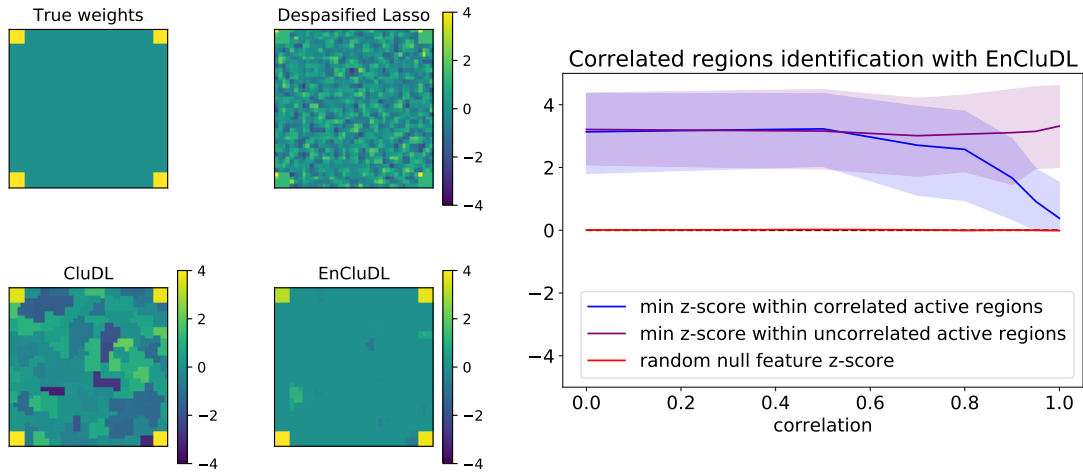


Figure 11: **Impact of correlation when trying to identify two correlated regions.** Left: True weight map, and z-scores estimated by Desparsified Lasso, CluDL and EnCluDL, obtained for $\rho = 0.9$. Desparsified Lasso cannot handle the extreme short-range correlation that occurs within each predictive region and only identifies one feature in each. CluDL and EnCluDL benefit from the clustering, as they identify all the features for every predictive regions. We can also observe that EnCluDL improves upon CluDL thanks to the smoothing effect produced by ensembling. Focusing on the EnCluDL solution, we can see that the z-score of the upper left active region is a bit lower than for the other active regions. This is due to the high correlation between the upper left and bottom right regions. Right: Summary of the results of the second simulation. When the correlation increases the minimum z-score within the correlated active regions decreases. The minimum z-score between the two uncorrelated regions is used as a control. We also plot the z-score of a random non-predictive feature, we notice that due to the ensembling step of EnCluDL, the empirical confidence intervals are much thinner than in Fig. 10. We observe that for a correlation lower than 0.8 the deviation is limited and it is possible to identify the two correlated predictive regions. For a correlation larger than 0.9 the deviation becomes large and recovering the two correlated regions becomes impossible.

1039 the design matrix \mathbf{X} , we first construct a 2D matrix $\tilde{\mathbf{M}}$ by drawing p random normal
1040 vectors of size n that are spatially smoothed with a 2D Gaussian filter (the smoothing is
1041 only made in the feature space for each sample independently, the samples are not mixed
1042 and remain independent). We flatten the vectors to go from $\tilde{\mathbf{M}}$ of size $n \times H \times H$ to \mathbf{M}
1043 of size $n \times p$. The spatial smoothing enforces a 2D structure on the data. Then, we further
1044 modify \mathbf{M} such that (i) all the features of an active region are perfectly correlated and
1045 (ii) two of the four active regions are correlated at a given value $\rho \in (0, 1)$, the two
1046 other active regions being unmodified (hence uncorrelated). The first transformation
1047 aims at showing that the clustering is useful to handle the short-range correlation that
1048 might be very high for fMRI data (see Sec. 7.4). The second transformation aims at

1049 testing whether EnCluDL can recover two correlated predictive regions; this is notably
 1050 desirable in the case of long-range correlation (*e.g.*, two contralateral brain regions). The
 1051 two uncorrelated regions are used to provide control values. With these transformations
 1052 we obtain the design matrix \mathbf{X} . In [Sec. 7.4](#), the two active regions that are correlated
 1053 are located in the upper left corner and in the bottom right corner while the other two
 1054 are uncorrelated. Finally, we also set $\sigma_\varepsilon = 10$, to approximately get $\text{SNR}_y = 4$.

1055 To check the ability of EnCluDL to identify two correlated regions, we compare
 1056 the smallest z-score of the features that belong to one of the correlated regions with the
 1057 smallest z-score of the features that belong to the uncorrelated active regions; we analyze
 1058 the results for several values of $\rho \in (0, 1)$. To understand the effect of the clustering and
 1059 ensembling, we compare Desparsified Lasso, CluDL and EnCluDL solutions qualitatively.
 1060 Since the features that belong to the same active region are perfectly correlated, we
 1061 expect that Desparsified Lasso identifies only one feature per region at best. We also
 1062 report the z-score of a random non-predictive feature.

1063 **Second simulation results.** In [Fig. 11](#), we give the results for the second simulation.
 1064 Clustering turns out to be crucial to produce valid statistical inference solution in the
 1065 presence of extreme short-range correlation. Additionally, we show that when the corre-
 1066 lation of the two correlated active regions increases, their identification using EnCluDL
 1067 becomes harder. In this experiment, we observe that below a correlation of 0.8, En-
 1068 CluDL can identify accurately the two correlated regions. However, above a correlation
 1069 of 0.9, EnCluDL generally fails to recover the two correlated regions.

1070 7.4 fMRI data structure

1071 In [Sec. 7.3](#), we have shown that one may encounter multicollinearity issues. It is thus
 1072 necessary to analyze the correlation structure of actual fMRI data.

1073 In [Fig. 12](#), we study the correlation observed in the HCP900 Emotion task data.
 1074 Considering correlation between random voxels, then neighboring voxels, we can see
 1075 that the correlation is much higher in the case of neighboring voxel. Notably, the median
 1076 correlation between two random voxels is 0.1 while the median correlation between two
 1077 neighboring voxels is above 0.8, and often larger than 0.9. We have shown in [Sec. 7.3](#), that
 1078 Desparsified Lasso may fail to detect two features when they are so strongly correlated.

1079 Correlation histograms after clustering the data as shown in [Fig. 12](#). For example,
 1080 taking $C = 500$ clusters, the median correlation between two random clusters is 0.3 while
 1081 it is 0.7 for two neighboring clusters. Inter-cluster correlation always remains below 0.85
 1082 and almost always below 0.8. In practice, we have shown in [Sec. 7.3](#) that Desparsified
 1083 Lasso can handle scenarios where features have correlation lower than 0.8.

1084 7.5 Estimating δ for which EnCluDL controls the δ -FWER

In [Sec. 3.5](#), we recommend using δ , in regular brain imaging settings with [\(12\)](#):

$$\delta_0 = \left(\frac{p}{2C} \right)^{1/3},$$

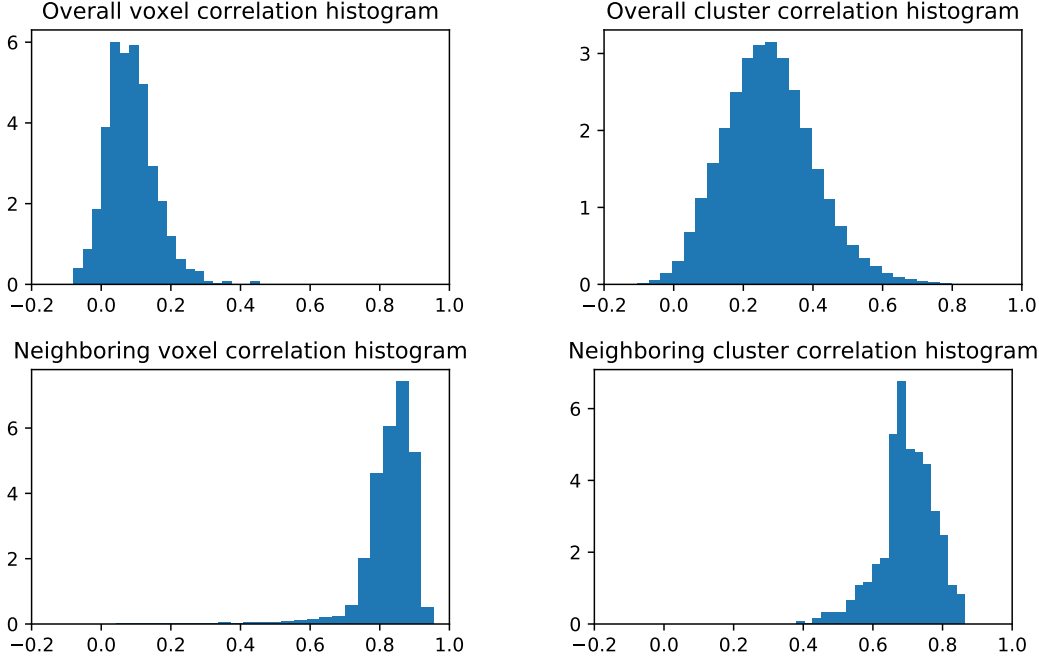


Figure 12: **Data structure in HCP900 emotion task.** Left: Correlation histogram of the fMRI data at voxel level. The correlation between two random voxels is quite low, a typical value being around 0.1. However, when looking at neighboring voxels, we observe that the correlation is often higher than 0.9. This exhibits the short- and long-range correlation structure but also suggests that raw Desparsified Lasso would not be adapted to this setting. Right: Correlation histogram of the clustered data for $C = 500$. The correlation between two random clusters is around 0.3, while the correlation between two neighboring clusters is around 0.7 and almost always below 0.8. Then, thanks to clustering, highly correlated voxels are aggregated into groups and Desparsified Lasso is adapted to this setting.

1085 δ_0 being a distance in voxel unit close to the average radius of the clusters used in En-
1086 CluDL. However, when the setting is particularly favorable for inference, *i.e.*, if $\log(n)/C$
1087 is large or σ_ε is small, the choice of δ given by (12) may be over-optimistic and we might
1088 need to correct this formula. We have found empirically that a suitable multiplicative
1089 factor, denoted by $\tau > 0$, that could be used to correct δ_0 is given by:

$$\tau = -45 \log \left(\frac{\sigma_\varepsilon}{\text{std}(\mathbf{y})} \right) \frac{\log(n)}{C}, \quad (22)$$

1090 where σ_ε is the standard deviation of the noise ε . In practice σ_ε has to be estimated; in
1091 the fMRI datasets we studied, estimates of $\frac{\sigma_\varepsilon}{\text{std}(\mathbf{y})}$ were close to 0.1. However, given the
1092 heuristic derivation of this quantity and the uncertainty about the value of τ , we do not
1093 recommend correcting δ_0 with a factor lower than 1 as it could lead to a dramatic under
1094 estimation of the valid δ . Then, the final formula to compute the δ such that δ -FWER

1095 control is ensured, is:

$$\delta^* = \max(1, \tau) \delta_0 . \quad (23)$$

1096 Note that the formula given by (12) and even (23) are not bullet proof but rather give
1097 reasonable estimates of δ .

1098 7.6 Cluster size analysis

1099 In Sec. 3.5, we have proposed a formula to compute a valid spatial tolerance parameter
1100 δ_0 . In Fig. 13, we show that δ_0 is close but slightly lower than the average cluster radius.
1101 Also, one can notice that taking a larger number of clusters, the size of the clusters is
1102 smaller. As a consequence, the statistical control is valid for a lower spatial tolerance.
1103 Finally, by looking at the shape of the distribution of the cluster radius, we observe that
1104 there are only few large clusters.

1105 In general δ_0 is a suitable choice, however when the setting is particularly favorable
1106 for inference, the mixing effect produced by ensembling might not be sufficient and voxels
1107 far (further than δ_0) from the support might be discovered. This effect can be explained
by the detection of large clusters that are overlapping the support and the null region.

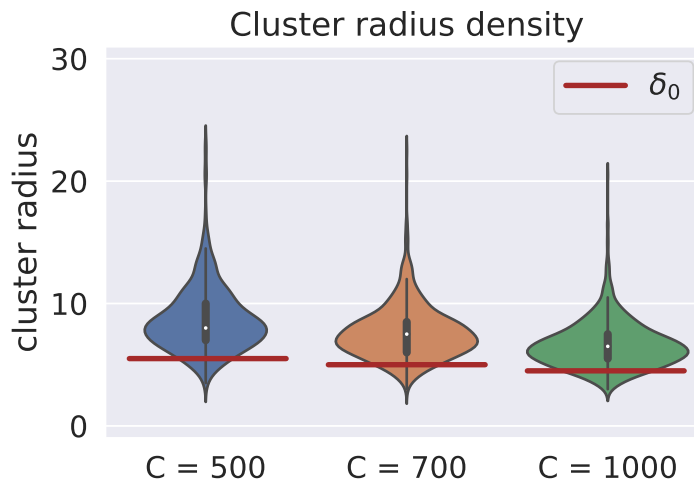


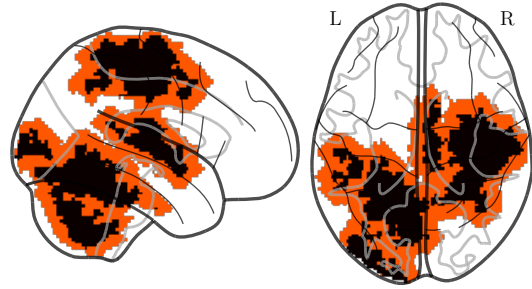
Figure 13: **Comparing δ_0 with the distribution of the cluster radius as a function of C .** By taking a larger number of clusters, we decrease the size of the clusters. The statistical control is thus valid for a smaller spatial tolerance. Comparing the distribution of the cluster radius with the recommended choice of spatial tolerance parameter δ_0 , we observe that δ_0 is a bit lower than the empirical average cluster radius. Finally, we observe that few clusters are much wider than the others, this may occasionally lead to false discoveries far from the support in high SNR scenarios.

1108

1109 **7.7 Illustrating spatial tolerance on real brain geometry**

1110 In Fig. 14, we display a brain pattern with spatial tolerance in the case of the HCP data.

Figure 14: **Expanding HCP maps by 6 voxels.** The black-colored voxels represent the positive weights of the reference map constructed in Sec. 4.2. The red-colored voxels are the δ -dilation of the previous map where $\delta = 6$ voxels, *i.e.*, the tolerance we have taken in all experiments. Then, δ -FWER controls the false discoveries made outside of the colored voxels (see also Sec. 3.1).



1111

1112 **7.8 Statistical control under the global null with autocorrelated data**

1113 **Experiment.** In this experiment, we study how the different procedures control the
1114 FWER when the data are temporally autocorrelated; hence violating the i.i.d. assump-
1115 tion. Notably, this is the case if the data correspond to fMRI signal recordings of one
1116 given subject during an acquisition. We consider data from the HCP900 resting-state
1117 fMRI dataset described in Sec. 4.1 with full samples ($n = 1200$). The design matrix
1118 \mathbf{X} contains the 15-minutes fMRI signal records. As in Eklund et al. [2016], we con-
1119 struct \mathbf{y} such that it corresponds to two activity paradigms: block or event responses,
1120 with several frequencies: 10s on/off, 20s on/off, 30s on/off, 2s-activation/6s-rest, 4s-
1121 activation/8s-rest. Thus, \mathbf{y} is temporally autocorrelated. In these simulations $\mathbf{w}^* = \mathbf{0}$
1122 so the δ -FWER and the classical FWER are identical. To better assess the impact of
1123 correlation, we also generate \mathbf{y} as an i.i.d. —uncorrelated— Bernoulli or standard Gaus-
1124 sian random variable (here again $\mathbf{w}^* = \mathbf{0}$), breaking spurious correlations between \mathbf{X}
1125 and \mathbf{y} . These two cases enable to check if the procedures still control the FWER at
1126 the targeted nominal level on this dataset under the i.i.d. hypothesis. For each kind of
1127 response, we repeat the experiment 100 times, using data from 100 different subjects.

1128 **Results.** we now report the results of the experiment. In Fig. 15, we observe that for
1129 all the fictitious block response paradigms, for every procedure, the empirical FWER ex-
1130 ceeds the targeted nominal level (10%), as one would expect. This result is not surprising
1131 since independence across samples is a key assumption for a valid statistical inference
1132 with any of the four procedures. Notably, concerning EnCluDL, Desparsified Lasso needs
1133 the i.i.d. hypothesis [Zhang and Zhang, 2014, van de Geer et al., 2014] to produce valid
1134 confidence intervals or p-values. This assumption is not verified for the block or event

1135 response paradigms due to the temporal dependency in the data. However, when the
 1136 target \mathbf{y} is i.i.d. —*i.e.*, without temporal dependency (Bernoulli or Gaussian random
 1137 responses)— the FWER is controlled (except for Thr-SVR). Indeed, the model is no
 longer confounded by the correlation structure underlying the data.

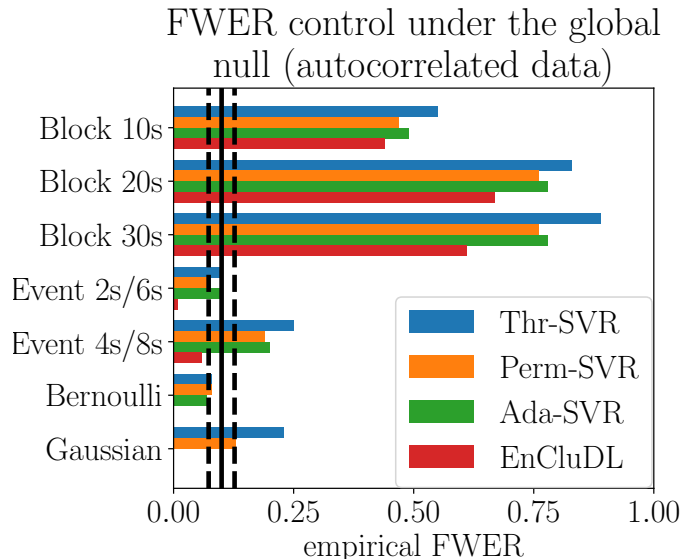


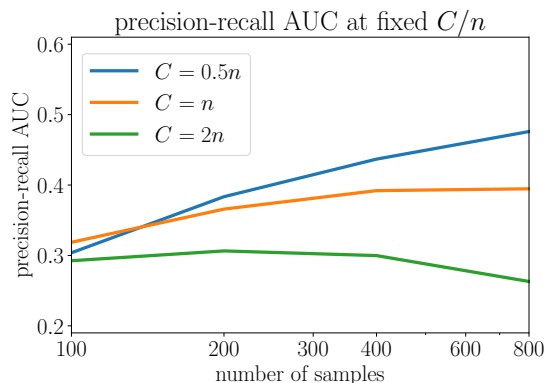
Figure 15: **FWER control under the global null with autocorrelated data.** The results of the experiment with correlated data under the global null, described in [Sec. 7.8](#), show that, when the data are temporally autocorrelated, all the procedures fail to control the FWER. Indeed, for all the fictitious block response paradigms, the empirical FWER exceeds the targeted nominal level of 10% for every procedure. This result is not surprising as the procedures control the δ -FWER under the hypothesis that the samples are i.i.d.; this is not the case for the block or event response paradigms. However, when the fictitious response breaks the temporal dependency (binary or Gaussian random responses), the i.i.d. hypothesis is met and the FWER is empirically well controlled except for the Thr-SVR procedure.

1138

1139 7.9 Influence of the C/n ratio on the recovery property of EnCluDL

1140 When using EnCluDL, the number C of clusters is an arbitrary parameter. We proposed
 1141 some default choice in [Sec. 4.5](#), yet intuitively, C should adapt to the amount of data
 1142 available: larger samples size lead to better estimation, allowing refined localization,
 1143 hence higher C . In [Fig. 16](#), we show on semi-simulated data that for $C \in [n/2, n]$, C/n
 1144 being fixed, the precision-recall AUC on real data does not depend on n , suggesting to
 1145 chose C proportional to n .

Figure 16: **Influence of the C/n ratio on the precision-recall AUC.** The results of the experiment described in Sec. 4.5 show that the precision-recall AUC depends almost linearly on $\log(C/n)$ except when C is critically low creating very wide clusters and deteriorating the precision-recall curve. This limit depends on the physical properties of the problem; here, C should not be lower than 100. Keeping this limit in mind, we advise taking $C \in [n/2, n]$ to recover most of the predictive regions.



1146 7.10 Statistical control with known ground truth: additional plots

1147 In this section, we provide additional experimental results to assess the detection accu-
 1148 racy of the multivariate estimators, to complement the results in Sec. 4.2. Fig. 17 shows
 1149 additional precision-recall curves, obtained for different values of n : these different set-
 1150 tings preserve the relative performance of the methods, while larger n results in better
 1151 curves. However, we do not recommend running such analysis with $n < 100$, since the
 1152 estimation problem is hard and statistical guarantees only hold in asymptotic regime.
 1153 Fig. 18 and Fig. 19 display the performance of the methods in terms of δ -FWER control
 1154 and precision-recall curves on semi-simulated data where \mathbf{y} is binary. This induces a vio-
 1155 lation of the EnCluDL model that reduces its performance in terms of δ precision-recall.
 1156 Yet, unlike Ada-SVR, it still controls the δ -FWER accurately.

1157 7.11 Face validity on HCP dataset

1158 In Fig. 23, we plot the results for five tasks taken from the HCP dataset, besides of the
 1159 two described in Sec. 4.6. For all methods, the statistical maps are thresholded such that
 1160 the δ -FWER stays lower than 10% for $\delta = 12$ mm. Qualitatively, EnCluDL discovers
 1161 the most plausible patterns, Ada-SVR often makes dubious discoveries, patterns are
 1162 too wide and implausible, while the two other methods exhibit a very weak statistical
 1163 power. As discussed in the main person, Univ-OLS provides complementary results that
 1164 highlight marginal association between the data and the target.

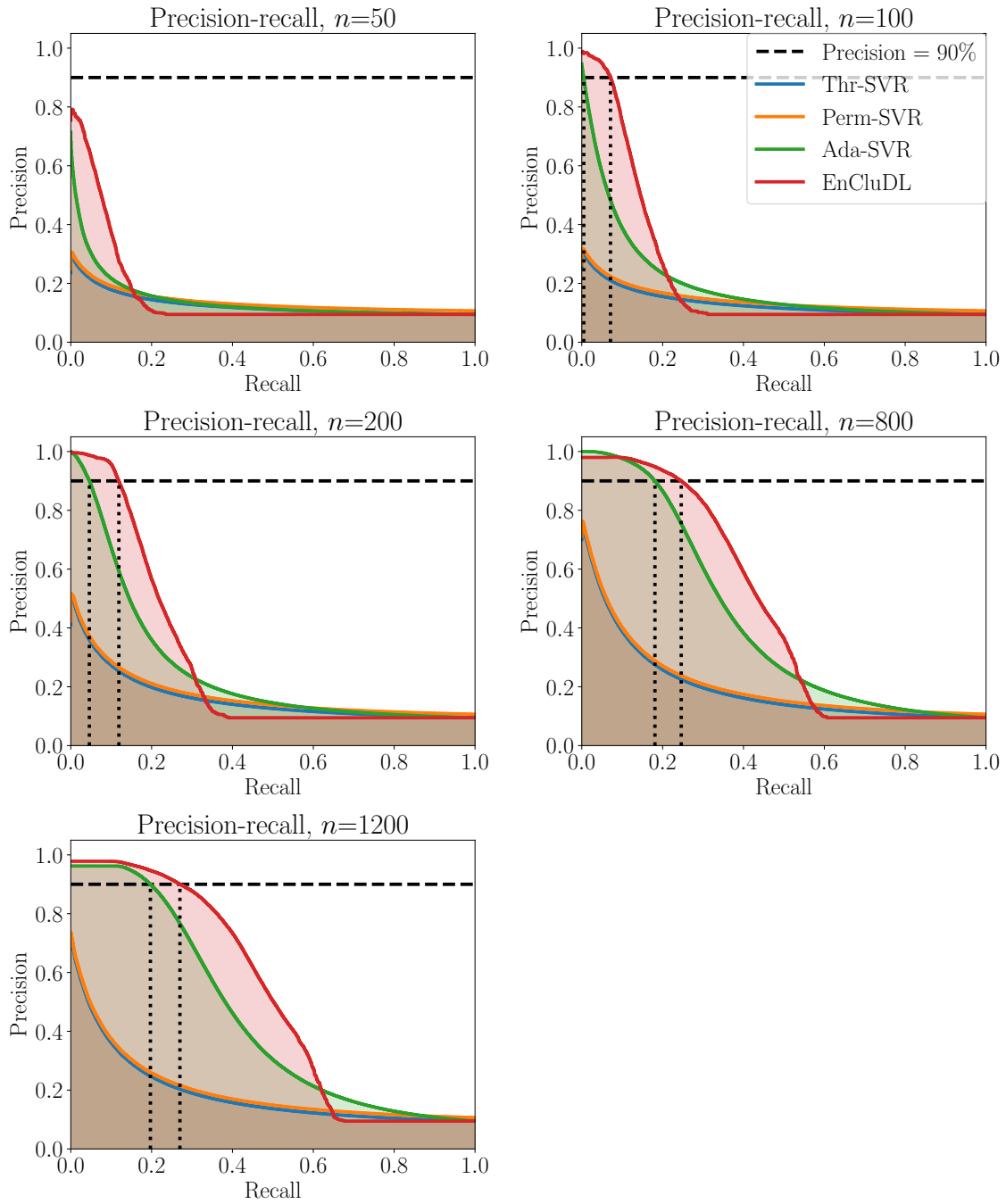


Figure 17: **Precision-recall curves on semi-simulated data with continuous response vector.** The results of the experiment described in Sec. 4.2 show that EnCluDL has the best performance in terms of precision-recall curve.

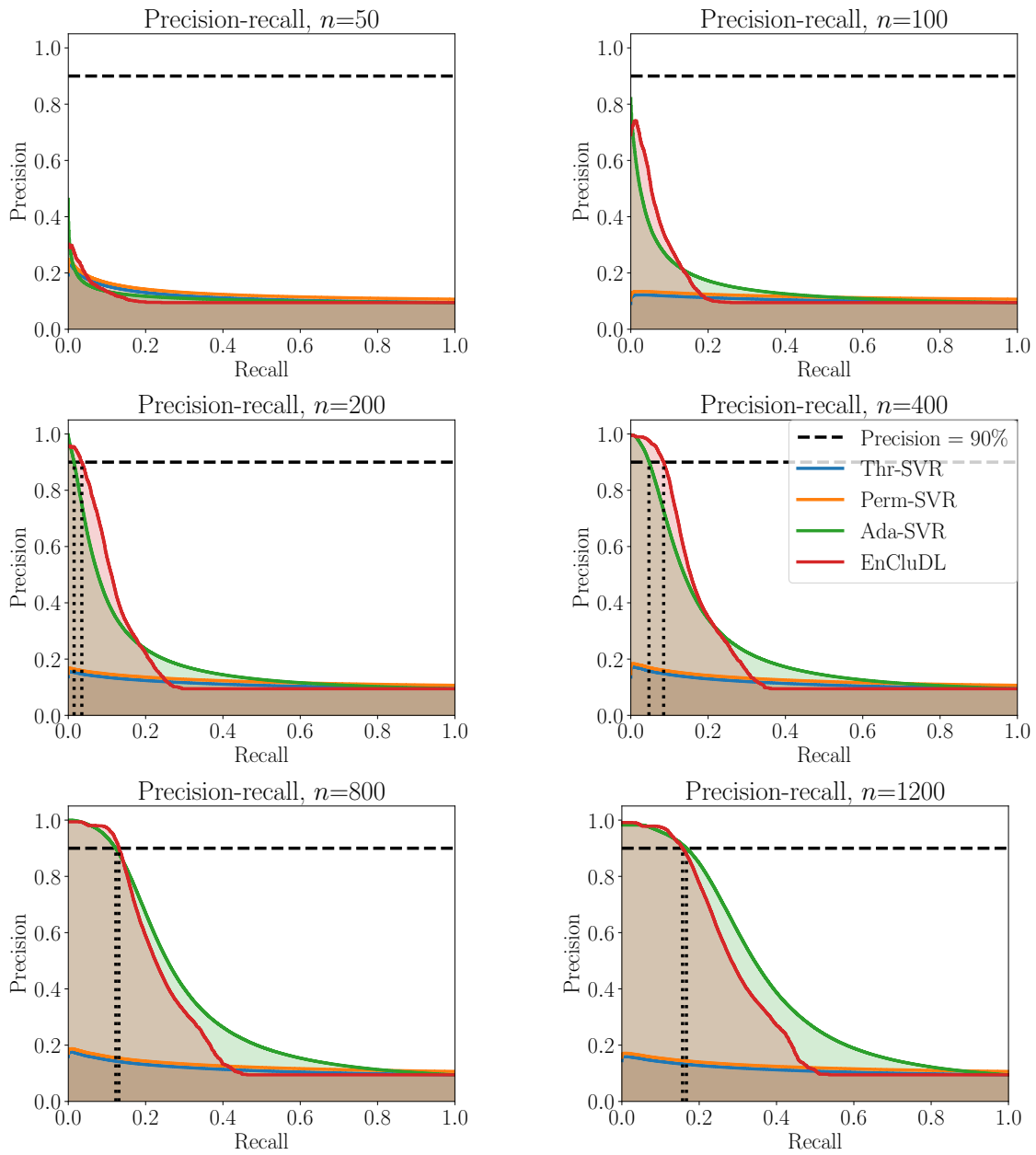


Figure 18: **Precision-recall curves on semi-simulated data with binary response vector.** The results of the experiment described in [Sec. 4.2](#) with binary response show that Ada-SVR and EncluDL outperform alternatives in terms of feature recovery. These results are quite similar to the one presented in [Fig. 6](#).

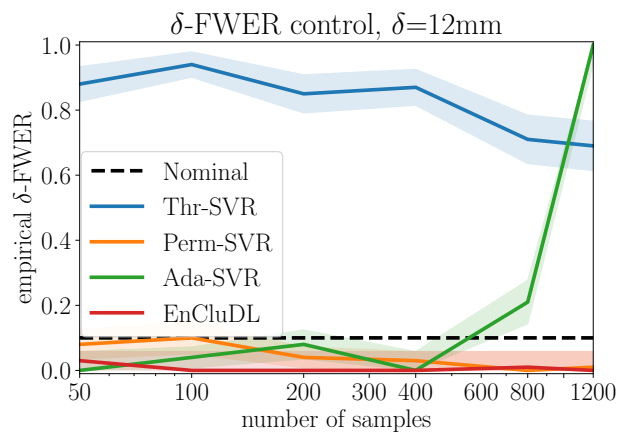


Figure 19: δ -FWER control on semi-simulated data with binary response vector. The results of the experiment described in Sec. 4.2 with binary response show that only Perm-SVR and EnCluDL actually control the .

δ -FWER.

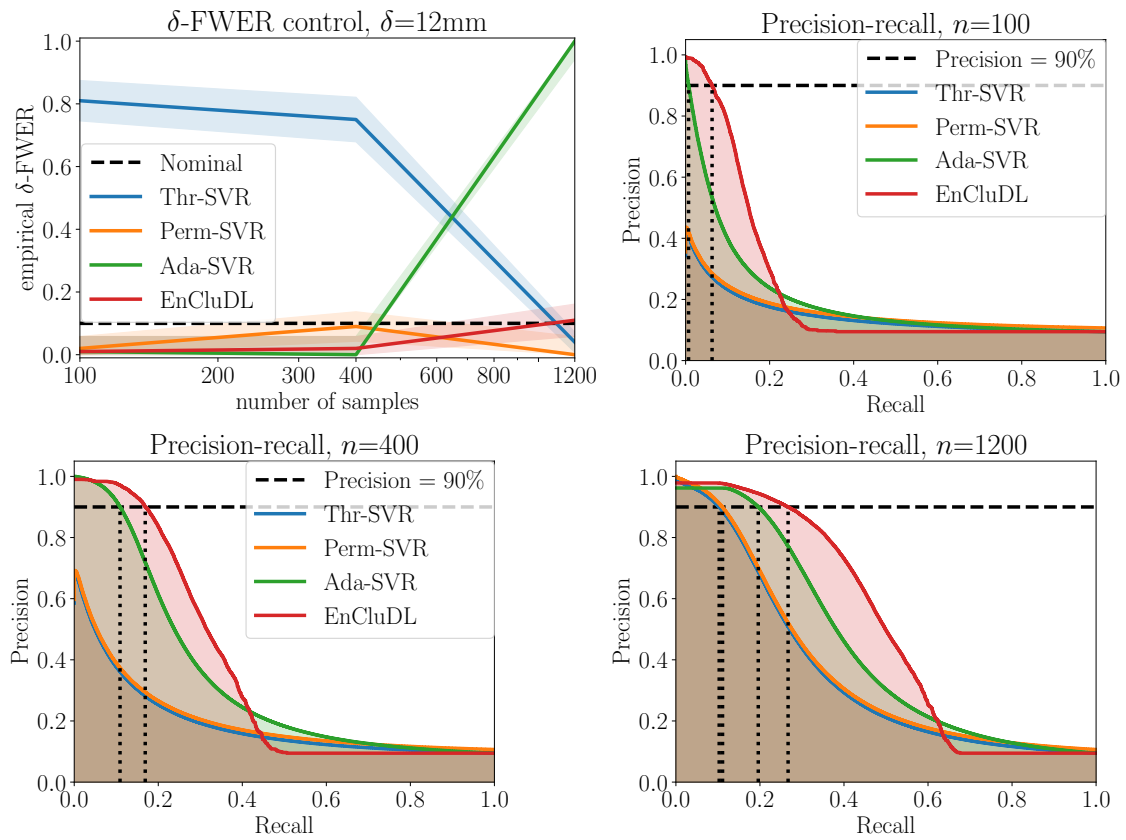


Figure 20: δ -FWER control and precision-recall curves on semi-simulated data with continuous response vector with Laplace noise. The results of the experiment described in Sec. 4.2 with Laplace noise are similar to the one presented in Fig. 6 for Gaussian noise.

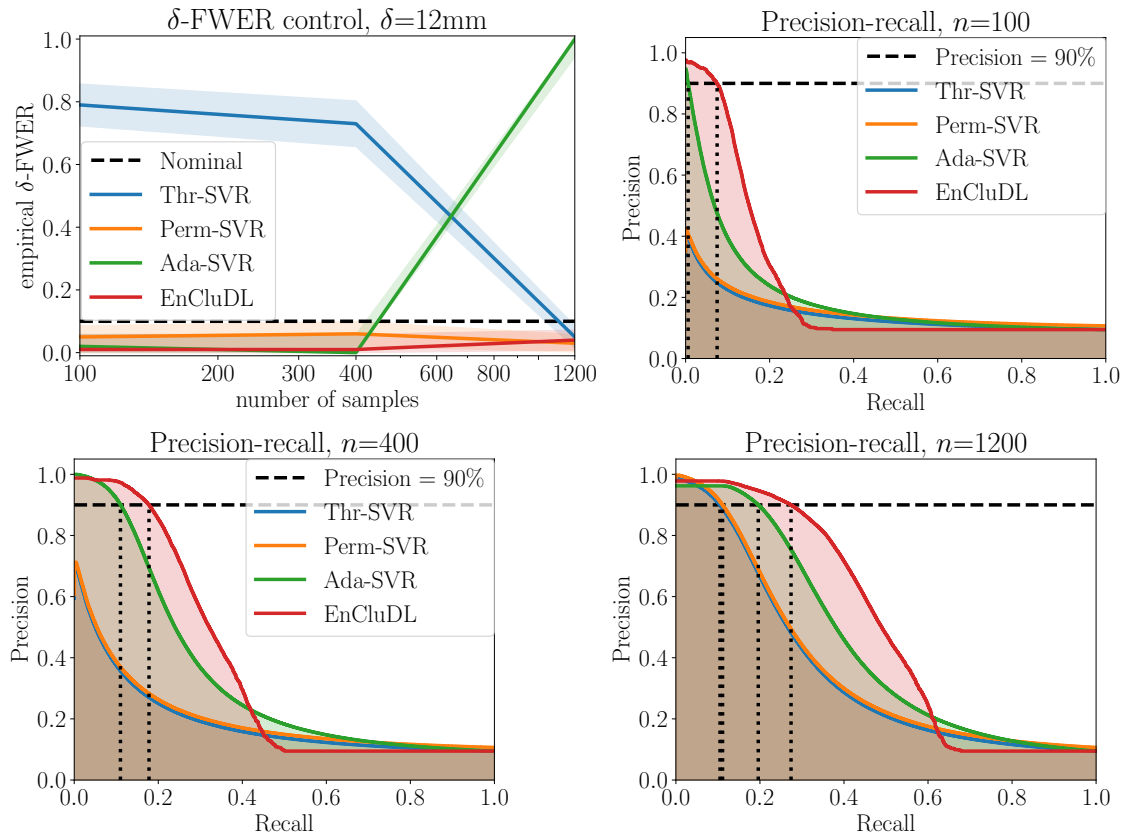


Figure 21: δ -FWER control and precision-recall curves on semi-simulated data with continuous response vector with Student noise. The results of the experiment described in Sec. 4.2 with Student (with 5 degrees of freedom) noise are similar to the one presented in Fig. 6 for Gaussian noise.

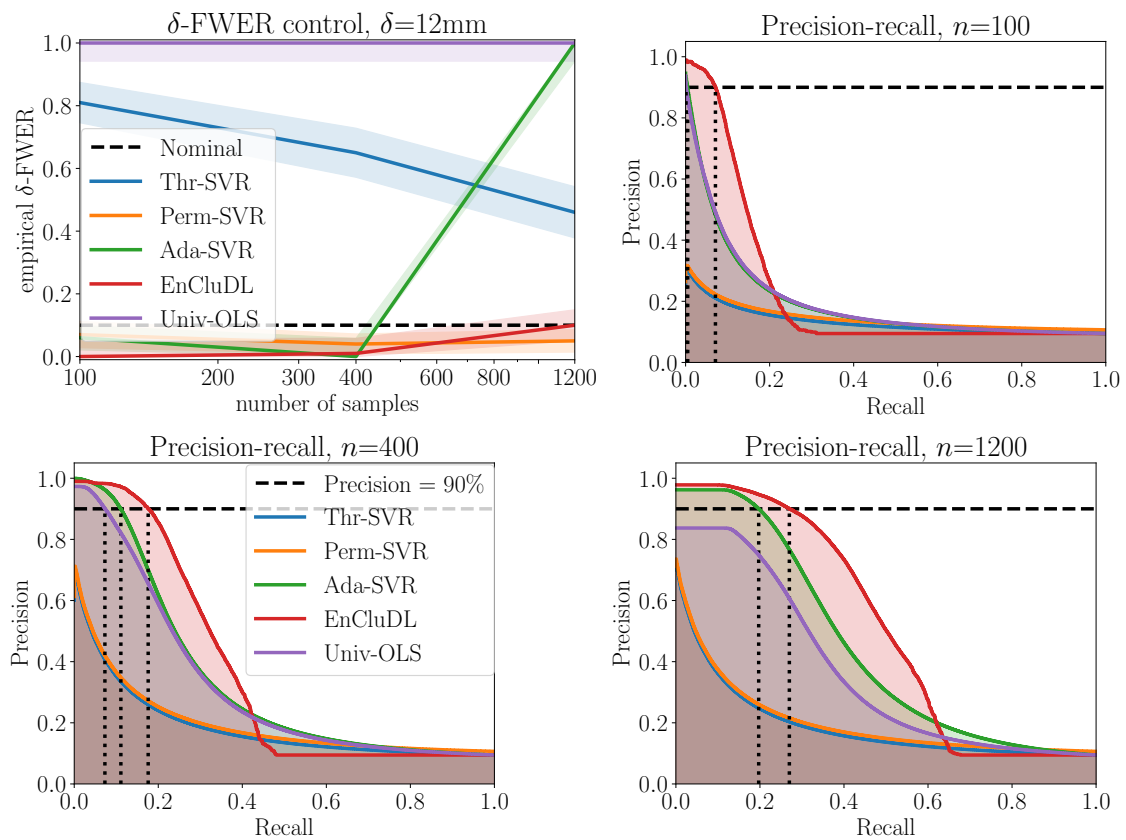
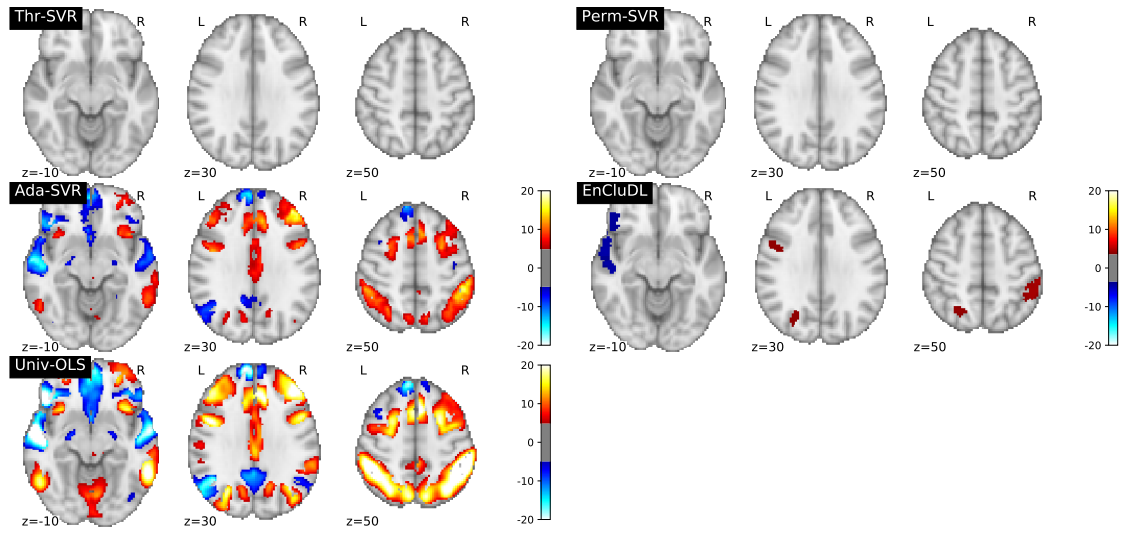
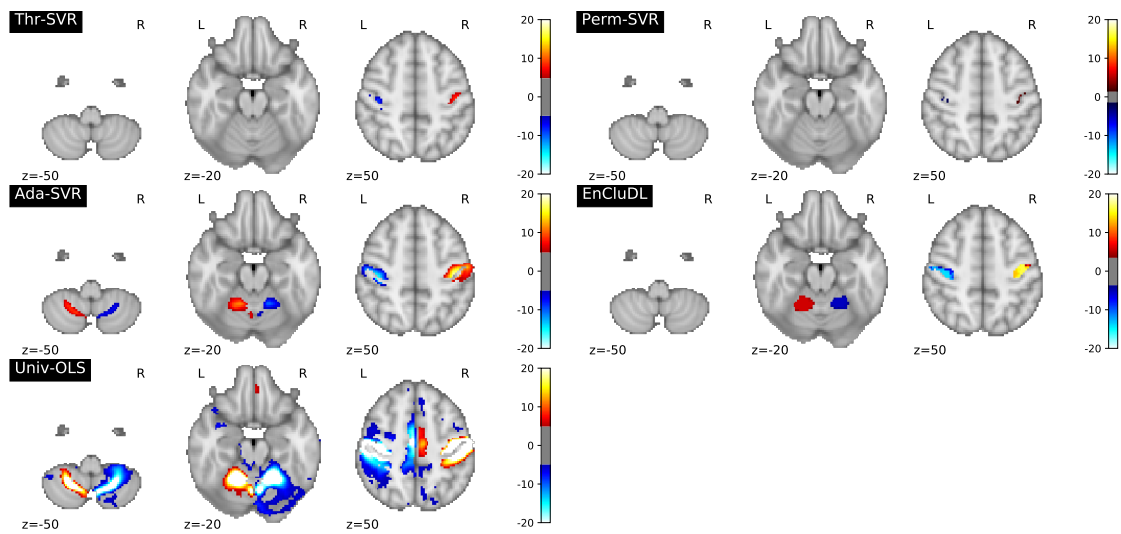


Figure 22: δ -FWER control and precision-recall curves on semi-simulated data with continuous response vector including a univariate method. These results show that the FWER control guaranteed by Univ-OLS for univariate inference does not match the control granted by EnCluDL in the conditional paradigm. This is due the fact that the null hypotheses being tested are not the same.

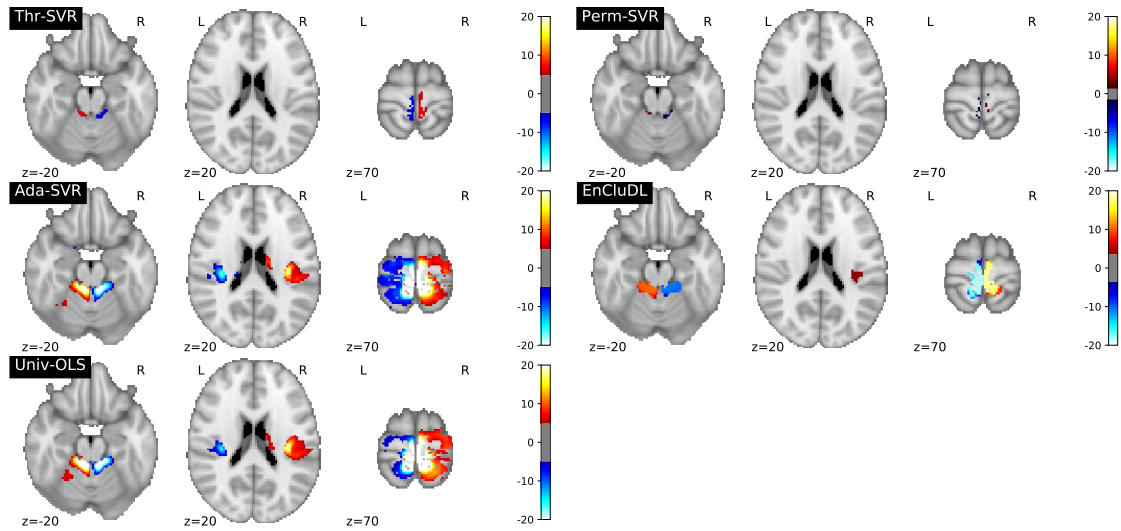


(c) Language

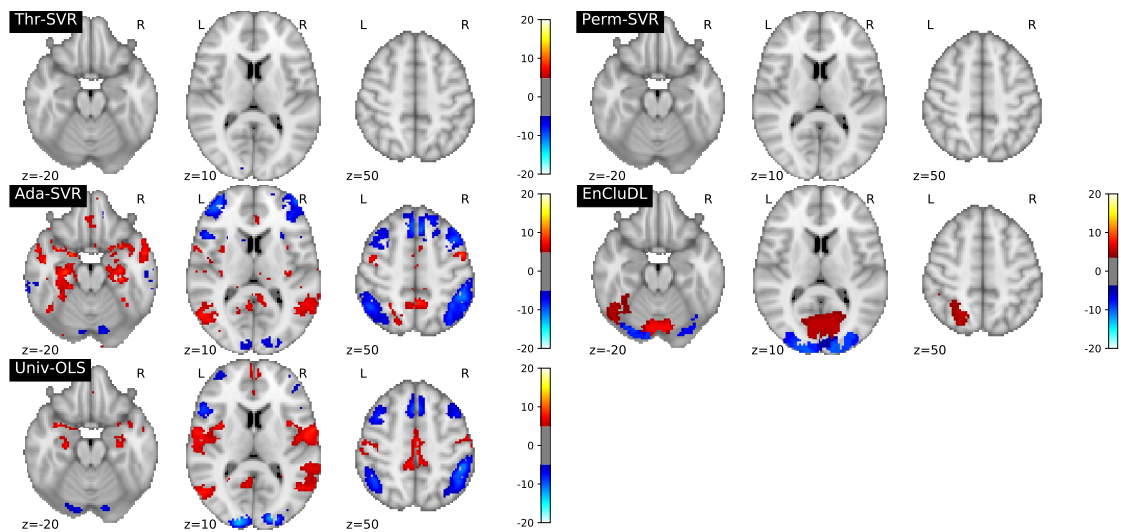


(d) Motor Hand

Figure 18a: cf. Fig. 23 for description.

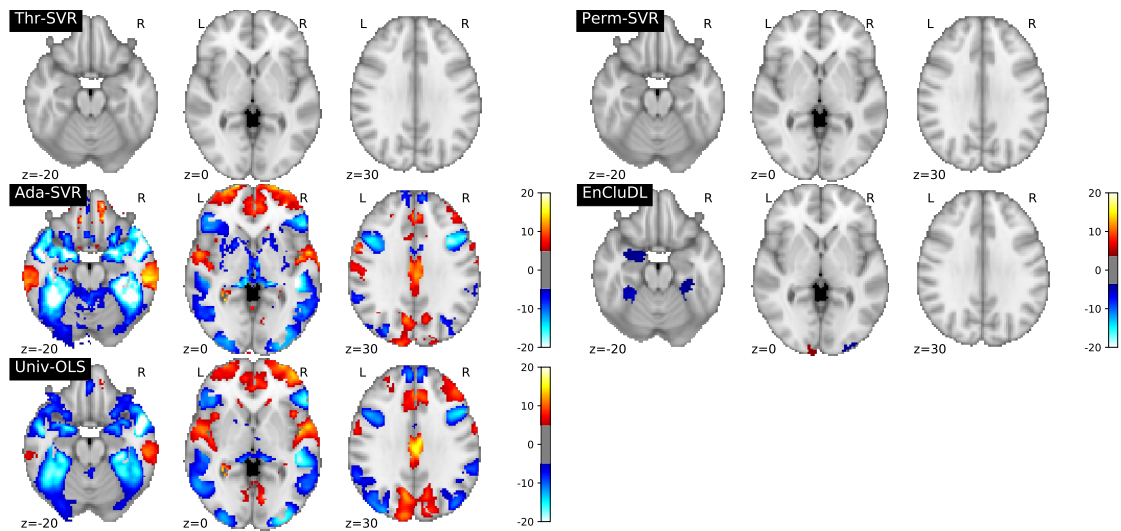


(e) Motor Foot



(f) Relational

Figure 18b: cf. Fig. 23 for description.



(g) Social

Figure 23: **Estimated predictive patterns on standard task fMRI dataset.** Here, we plot the results for five tasks of the experiment described in [Sec. 4.6](#) thresholding the statistical maps such that the δ -FWER stays lower than 10% for $\delta = 12$ mm. Qualitatively, EnCluDL discovers the most plausible patterns, Ada-SVR often makes dubious discoveries, patterns are too wide and implausible, while the two other methods exhibit a very weak statistical power. As discussed before, Univ-OLS provides complementary results that display marginal associations between voxel signals and the target. The results of emotion and gambling tasks are available in [Fig. 7](#).

1165 **7.12 Prediction performance**

1166 In this section, we give results on the prediction performance of the methods. In **Fig. 24**,
 1167 we plot the results of the experiment described in **Sec. 4.7**. We notice that the classifica-
 1168 tion error rate is almost the same for SVR (the weight map of Thr-SVR and Perm-SVR)
 1169 and Ada-SVR, their prediction performance is slightly better than the one of EnCluDL.
 1170 Hence, we do not recommend using EncluDL to achieve state-of-the-art prediction ac-
 curacy, but only for statistical inference purpose.

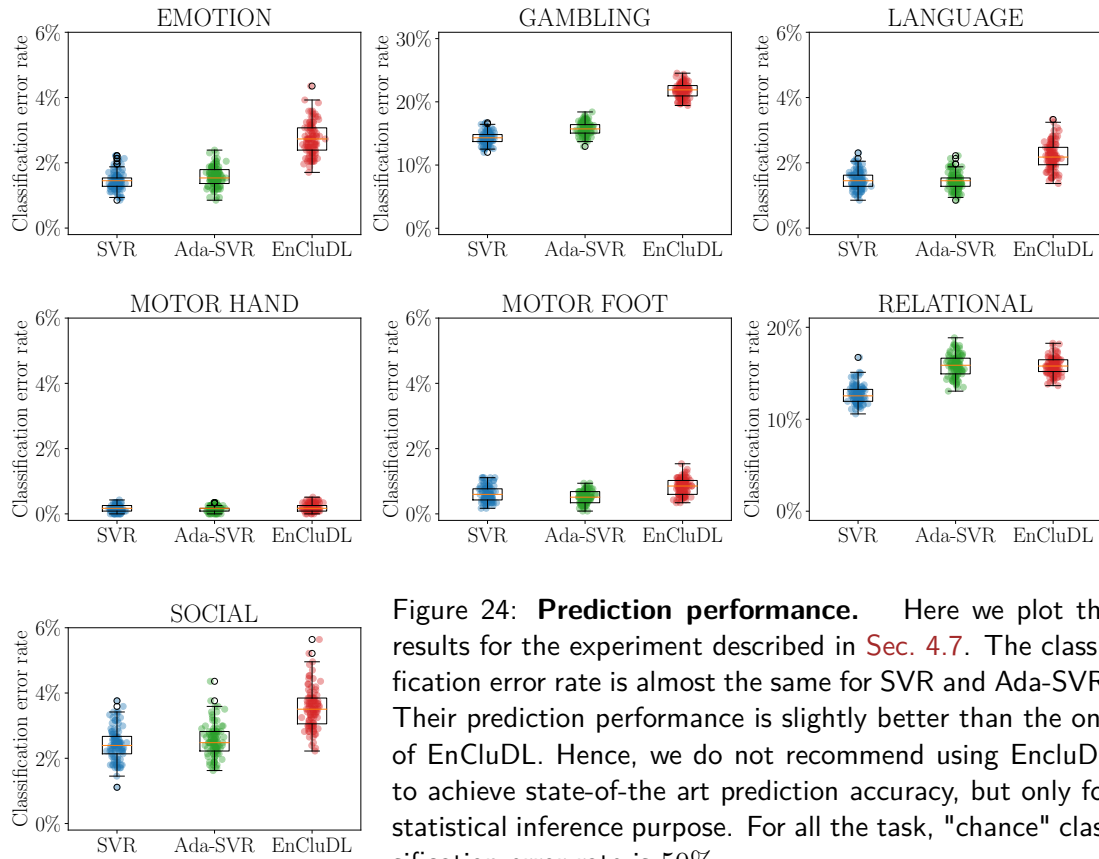


Figure 24: Prediction performance. Here we plot the results for the experiment described in **Sec. 4.7**. The classification error rate is almost the same for SVR and Ada-SVR. Their prediction performance is slightly better than the one of EnCluDL. Hence, we do not recommend using EncluDL to achieve state-of-the-art prediction accuracy, but only for statistical inference purpose. For all the task, "chance" classification error rate is 50%.

1171