Title:

Addicted or not? A new machine learning-assisted tool for the diagnosis of addiction-like behavior in individual rats

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Keywords:

Severe substance use disorder, individual vulnerability, machine learning, clustering, neural networks, addiction

Abstract:

Background: The transition from controlled to compulsive drug use occurs in a small proportion of individuals characterizing substance use disorder (SUD). The "3-Criteria" model developed on the operationalization of key DSM diagnostic criteria of SUD has helped to shed light on behavioural and biological factors involved in these divergent trajectories. However, the classification strategy on which the model has hitherto relied puts as much weight on the cohort to which the individual belongs as on their own characteristics, thereby limiting its construct validity with regards to the individual-based diagnostic approach in humans.

Methods: Large datasets resulting from the combination of behavioral data from several of our previous studies on addiction-like behavior for cocaine or alcohol were fed to a variety of machine learning algorithms (each consisting of an unsupervised clustering method combined with a supervised machine learning algorithm) in order to develop a classifier that identifies

resilient and vulnerable rats with high precision and reproducibility irrespective of the cohort to which they belong.

Results: A classifier based on K-median or K-mean clustering (for cocaine or alcohol, respectively) followed by Artificial Neural Networks emerged as the best tool reliably and accurately to predict if a single rat is vulnerable or resilient to addiction as operationalized in the 3-Criteria model. Thus, all the rats previously characterized as 0 or 3crit in individual cohorts were correctly labelled as Resilient or Vulnerable, respectively, by this classifier.

Conclusion: The present machine learning-based classifier objectively labels single individuals as resilient or vulnerable to develop addiction-like behaviour in multisymptomatic preclinical models of cocaine or alcohol addiction in rats, thereby increasing their heuristic value with regards to the human situation.

Introduction:

All individuals who regularly take addictive drugs do not necessarily lose control over drug intake and develop the persistent, compulsive drug seeking and taking that characterizes severe substance use disorder (SSUD) **(Figure 1)** (1). Thus, as long suggested by Hyman and Malenka (2), while it is important to understand the mechanisms underlying the initiation and maintenance of drug use, it is pivotal to understand the mechanisms, in a subset of vulnerable individuals, that mediate the vulnerability to switch from controlled, recreational drug use to SSUD. This individual vulnerability has long been suggested to stem from the interaction between environmental, sociodemographic, psychological, neurobiological and behavioral factors (3-10). However, investigating the role of these factors in humans is fraught with difficulty not least because such an endeavor requires the study, in relatively controlled conditions, of large populations across the lifetime, with little if any opportunity to establish causation or carry out the invasive manipulations that are necessary to understand the underlying neural and cellular mechanisms.

Over the past two decades, preclinical models have progressively evolved to incorporate the importance of these individual differences, thereby offering unique opportunities to overcome these limitations by using prospective longitudinal studies to investigate the psychological and neural basis of the vulnerability to develop addiction-like behavior (11). Such a paradigm shift has been made possible by the development of new behavioral procedures that operationalize key clinical features of SSUD, including the persistence of drug-related activities in the face of adverse consequences (11, 12).

As an initial foray into the development of such procedures (11), we published in 2004 a multidimensional model in rats (coined as the 3-Criteria model) (12) in which addiction-like

behavior for cocaine is identified in a subset of a population stratified on specific behavioral characteristics based on the operationalization of DSM-IV diagnostic criteria (13), namely, (i) increased motivation to take the drug, (ii) inability to refrain from drug seeking and (iii) maintained drug use despite aversive consequences.

This approach enables the identification of divergent trajectories with regards to the transition from controlled to compulsive drug intake (**figure 1**), in that only 15 to 30% of a given population of outbred rats exposed to cocaine will eventually display the three behavioral criteria of addiction following a prolonged (at least 60 daily sessions) history of self-administration. Importantly, the rats identified as displaying the 3-Criteria for addiction also show an increased tendency to escalate their drug intake when access is illimited, and they are prone to relapse following abstinence (14), thereby displaying additional behavioral features of addiction for which they have not been selected. The construct and predictive validity of the model was further substantiated by the fact that these differences between vulnerable and resilient rats are not due to a differential cocaine exposure since all rats had self-administered the same amount of drug prior to being identified as having 3 vs 0 criteria (12). However, even if they did not take more cocaine, the 3crit rats develop a burst-like, or binge-like pattern, that precedes the transition to addiction (14).

Capitalizing on the more classical drug-centered view that has shaped our understanding of the neurobiological basis of drug reinforcement, or the long-term adaptations to drug exposure such as those involved in the emergence of negative emotional states during withdrawal (15) and the progressive increase in drug intake that accompanies the history of drug use, procedures such as those on which the 3-Criteria model relies, have revealed that the brain mechanisms mediating the transition to addiction are not necessarily similar to those involved in acute or chronic response to drugs. For instance, while a single or several (often experimenter-delivered) administrations of cocaine promote synaptic plasticity in the mesolimbic system (16, 17) it is an inability to recruit adaptive synaptic plasticity in response to chronic drug self-administration that characterizes the vulnerability subsequently to develop addiction-like behavior (18). In addition, while endocannabinoid dependent LTD is observed in the prelimbic cortex in all individuals self-administering cocaine, mGluR2/3-dependent LTD in this structure is abolished exclusively in rats demonstrating addiction-like behavior, thereby demonstrating that the transition to addiction is underlined by a specific lack of plasticity in corticostriatal circuits (19), in line with recent evidence in humans (9, 10). Together these observations demonstrate that the tendency to persist in seeking and taking the drug despite adverse consequences is associated with a rigidity, not an exacerbation, of drug-induced synaptic plasticity in the corticostriatal circuits.

At the behavioural level, the 3-Criteria model has also been instrumental for the demonstration that high impulsivity (20) and boredom susceptibility (21) as assessed in the 5-choice serial reaction time task and a novelty-induced place preference task respectively, confer a vulnerability to switch from controlled to compulsive cocaine intake whereas sensation seeking, as assessed as a high locomotor response to novelty (20) and sign tracking (22) predict an increased tendency to take drugs or respond to drug paired cues while conferring resilience to addiction (20, 22).

These observations in rats have paved the way for studies in humans involving recreational users, individuals with SSUD, their siblings and drug naïve controls which, have eventually confirmed that in humans too the factors associated with recreational cocaine use are dissociable from those specifically associated with the transition to SUD (23). Importantly, the evidence of a causal relationship between a high impulsivity trait and the subsequent vulnerability to develop compulsive behaviours (Belin et al., 2008, Ansquer et al., 2015) has far reaching implications for our understanding of the neural basis of addiction. Because a high impulsivity trait has been shown to be underlined by a lower level of expression of D2-dopamine receptors in the mesolimbic system (24, 25), thereby demonstrating that the lower striatal D2 dopamine receptors that have been shown to be associated with a higher subjective response to stimulant drugs (26), is actually a marker of vulnerability to addiction, and not a neurobiological signature of the disorder, as initially suggested (26).

Overcoming the inherent correlational nature of human studies (26), the 3-Criteria model has also recently enabled the demonstration that the psychoaffective state of the individual at the time of initiation of drug self-administration, which can be shaped by contextual or broader environmental constrains, profoundly influences the vulnerability to develop SSUD (22).

This multidimensional approach has since been replicated and applied to the study of the neural and psychological basis of the vulnerability to develop alcohol use disorder (AUD) (27, 28) or food addiction (29). The individual tendency to persist in seeking or taking cocaine or to drink alcohol in the face of punishment or highly rewarding alternative reinforcers has further helped to identify the role of hypo-serotoninergic states in the vulnerability to develop compulsive cocaine seeking (30) and that of the GABA transporter GAT-3 in the amygdala in the vulnerability to AUD in both rats and humans (31, 32).

Together these data illustrate the high translational value of novel preclinical models that encapsulate the multi-dimensional nature of SSUD and the importance of focusing on the individual. However, these procedures are all dependent on the definition of a threshold above which a behaviour is deemed maladaptive, but where should the cursor be placed on a continuum to consider a behavioural response to be abnormal? For example, in the 3-Criteria

model the threshold for classifying individuals as having SSUD is determined by the physical properties of the distribution of the population for the resistance to punishment (12, 20, 21, 33). The bimodal distribution of resistance to punishment offers an objective threshold selection for this criterion, but its application to the two other criteria, which both follow a log-normal distribution, relies on the assumption that a similar rupture in the continuum exists in these criteria too, which is an inherent limitation to the model. In addition, a distribution-based threshold selection to classify individuals as being resilient or vulnerable to develop SSUD puts too large an emphasis on the population to which each individual belongs, the physical properties of which contribute almost equally to the characteristics of the individual in its classification. This precludes the determination of the vulnerability status of a given individual considered outside a particular cohort, which is another limitation in the construct validity of the model.

Recent developments in machine learning may offer unprecedented means to overcome these limitations as they have been suggested to help to refine the classification of individuals, including psychiatric patients, within specific sub-groups with shared underlying endophenotypes in order to tailor treatment strategies in a personalized medicine approach (34). Thus, here we applied machine learning to refine the classification of individual rats, trained in the 3-Criteria models of cocaine or alcohol addiction, as being either resilient or vulnerable. For this we subjected the individual scores in each of the three addiction-like behaviours to different clustering algorithms and then validated the labels using supervised machine learning algorithms.

Materials and Methods:

Data:

For addiction-like behavior for cocaine, data from 3 published papers (14, 20, 21) were pooled, representing an overall cohort of 88 individuals. For addiction-like behavior for alcohol, the data were pooled from 2 published (27, 28) and 1 unpublished experiment with an overall cohort of 150 rats.

All analyses were processed and analyzed using Python 3.8 (Python Software Foundation, Wilmington, DA, U.S.) using Numpy, Pandas and Scikit-learn packages as well as TensorFlow Keras for deep learning methods (35, 36). The code and the data sets are freely available at _____.

The total number of active lever presses performed in each of the three behavioral screens namely, (i) increased motivation to take the drug, (ii) inability to refrain from drug seeking and (iii) maintained drug use despite aversive consequences (compulsivity), were used as the

three variables, or dimensions, injected in the algorithms. It is important to note that the present analysis uses total number of responses performed by the rats while in the original experiments for addiction-like behavior for cocaine, the score for compulsivity was expressed as a percentage of baseline, while the last completed ratio in the progressive ratio test was considered to assess motivation.

The large datasets were split 50 times in 50 different training (67%) and test sets (33%) in order to avoid a cohort-driven bias in the clustering of the individuals **(Figure 2①)**.

Algorithm:

Individuals consuming drugs can be categorized as being vulnerable or resilient to develop SUD, and then present a specific severity along a clinical continuum if diagnosed by DSM (10, 37, 38), suggesting that any population could be segregated along two clusters. Nevertheless, the optimal number of clusters to be used in the classifier was determined by subjecting the 50 training and 50 test sets (i.e. 100 sets) to the Silhouette algorithm in order to inform the expected number of clusters based on the actual experimental dataset **(Supplementary data: cluster_number_cocaine.py, cluster_number_alcohol.py)**. The optimal number of clusters identified as the one most commonly informed by the Silhouette algorithm across the 100 iterations, was included as an input variable in the clustering algorithms of the classifiers tested in the study.

The behavioral data of a single pair of TRAINING set and TEST set was subjected to Unsupervised Clustering algorithms **(Figure 2②,③)** (namely Gaussian Mixture Model (GMM) or K-mean/ K-median clustering) to determine resilient and vulnerable rats in both sets **(Figure 2④,⑤)**.

GMM clustering (39) was used to mimic the bimodal threshold logic used in the 3-Criteria model since it is ideal for determining clusters when the central limit theorem cannot be applied and the data distribution shows bi/multimodal distribution. K-mean/K-median clustering algorithms were used for their relative ease of implementation, their ability to identify clusters of different shapes and sizes as well as their scalability (40).

The initial clustering step resulted in labelling of rats as Resilient and Vulnerable in both TRAINING and TEST sets **(Figure 2④,⑤)**.

We used four Supervised Classification algorithms namely, K nearest neighbor (KNN), Logistic Regression (LR), Support Vector Machines (SVM) and Artificial Neural Networks (ANN) to fit the behavioral data of the TRAINING SET and the labels for the rats assigned by the clustering algorithm to generate a mathematical model that best explains the behavioral

data and the labels of the rats in the TRAINING SET **(Figure 2⑥)**. Then, to predict the labels of the rats belonging to the TEST set, the behavioral data of the TEST SET rats were submitted to the mathematical model **(Figure 2⑦)** generated by each of the four Supervised Classification algorithms that were tested.

K nearest neighbor generates a mathematical model for the rats of the TRAINING SET behavioral data and the labels assigned by the clustering algorithm based on the KNN rule that states that similar data points are closer and hence belong to the same group (40). By submitting the behavioral data of the TEST set rats to this mathematical model, their labels are predicted based on how closely they resemble the TRAINING SET data points.

The logit function used in Logistic regression generates a mathematical model by mapping between 0 and 1 the behavioral data of the TRAINING SET rats and the labels assigned by the clustering algorithm. When the behavioral data of the TEST SET rats is submitted to this mathematical model, their labels as Resilient or Vulnerable are predicted by where they fall on the linear equation output between 0 and 1 with the cut off being 0.5 (41).

Support Vector Machines generate a mathematical model from the behavioral data of the TRAINING SET rats and the labels assigned by clustering algorithms by identifying a hyperplane in a multidimensional vector space such that the distance between the nearest points of the two groups from the hyperplane is maximized. When the behavioral data of the TEST SET rats is submitted to this mathematical model, the vulnerability label of each rat is determined by their location in the vector space with respect to the aforementioned hyperplane (35).

Finally, supervised Artificial Neural Networks take the behavioral data of the TRAINING SET rats and pass it through a feed-forward network of hidden neurons starting with random weights to calculate a 'cost function' eventually to assign labels as resilient and vulnerable to these rats. Back-propagation adjusts the weights of the hidden layer neurons to minimize this 'cost function' to adjust these labels and get as close to the labels of the TRAINING SET rats as assigned by the clustering algorithm as possible (**Figure 3**). A mathematical model is thus generated to best explain the behavioral data of the TRAINING SET rats and the labels assigned to them by the clustering algorithm.

When submitted to this mathematical model, the behavioral data of the TEST SET are used to ascribe resilient or vulnerable label to each rat of the TEST SET **(Figure 2⑧)** (35). Thus, one rat in the TEST set is ascribed two labels, one by the unsupervised clustering algorithm and one by a particular supervised prediction algorithm. The goal of this approach is to

determine the Unsupervised Clustering–Supervised prediction combination that yields overlapping labels for the TEST SET rats **(Figure 2⑨)**.

Performance evaluation metrics:

The labels assigned to the rats in the TEST set by the clustering algorithm (considered here as true labels) and the predicted labels of the same rats in the TEST set by supervised prediction algorithm can be represented in a classification matrix (Table 1).

Table 1: Classification Matrix

	Vulnerable (Supervised classification-based predictions- Test dataset)	Resilient (Supervised classification-based predictions- Test dataset)
Vulnerable (Unsupervised Clustering: test dataset)	True Vulnerable (TV)	False Resilient (FR)
Resilient (Unsupervised Clustering: test dataset)	False Vulnerable (FV)	True resilient (TR)

The following evaluation metrics were measured:

Accuracy: The proportion of rats from the TEST SET correctly predicted by the Supervised Classification algorithms compared to the labels given by the clustering algorithms

$$\textbf{Accuracy} = \frac{TV + TR}{TV + TR + FV + FR}$$

Precision: Of all the rats predicted as Vulnerable for the Supervised Classification algorithms, how many were also labelled as Vulnerable by the Clustering algorithms. The higher the precision, the lower the proportion of rats falsely predicted as vulnerable (false vulnerable)

$$\textbf{Precision} = \frac{TV}{TV + FV}$$

Recall (Sensitivity): Of all the rats labelled as Vulnerable by the Clustering algorithm, how many were correctly identified as Vulnerable by the Supervised Classification algorithm

$$\text{Recall} = \frac{TV}{TV + FR}$$

AUC ROC score: The Receiver Operating Characteristics (ROC) curve (42) plots the False Vulnerable rate [FV/ (TR+FV)] (1-precision) on the X-axis versus the True Vulnerable rate [TV/(TV+FR)] on the y-axis for several candidate threshold values between 0 and 1. The AUC ROC score is a useful tool to compare different classification models since it demonstrates the change in the relationship between precision and recall by varying the threshold to identify a TV rat.

Each pair of TRAINING and TEST SETS were subjected to this pipeline four times i.e. clustering with GMM followed by the four supervised prediction algorithms. As mentioned previously, there were 50 pairs of TRAINING and TEST sets so that for each combination of GMM clustering - supervised prediction algorithm, fifty iterations were processed resulting in fifty Accuracy, Precision, Recall and AUC ROC scores. Similarly, the same procedure was followed for K median/K mean clustering followed by the four supervised prediction algorithms. The results are depicted as kernel density estimates of the probability density function of these fifty iterations for all four performance evaluation metrics for each combination of unsupervised clustering-supervised prediction algorithm.

Results:

For addiction-like behavior for cocaine, Silhouette score revealed that the optimal number of clusters was '2' in 88% (Training sets – K-median clustering), 76% (Test sets – K-median clustering), 74% (Training sets- GMM clustering) and 76% (Test sets – GMM clustering), while the second most commonly suggested cluster number ranged from 3 to 6. Similarly, for addiction-like behavior for alcohol, Silhouette score revealed that the optimal number of clusters was '2' in 74% (Training sets – K-mean clustering), 78% (Test sets – K-mean clustering), 96% (Training sets- GMM clustering), 70% (Test sets – GMM clustering), while the second most commonly suggested cluster number ranged from 3 to 6. This analysis confirmed that 2 clusters should be used in subsequent analyses.

For addiction-like behaviour for cocaine, the K median-ANN based classifier (**Supplementary data: Kmedian_cocaine.py**) resulted in higher median accuracy (0.94), recall (1) and ROC AUC score (0.94) than the other K median-supervised algorithm-based classifiers **(Figure 4)**.

This classifier's superiority was also supported by the higher proportion of its iterations that reach accuracy (68%), recall (88%) and ROC AUC score (64%) in the top 10 percentile (between 0.9 and 1) compared to other K-median-based classifiers (**Table 2A**).

Considering GMM as a clustering method, combined GMM-ANN based classifier **(Supplementary data: GMM_cocaine.py)** resulted in higher median accuracy (0.89) and median precision (1) than the alternatives. This classifier's superiority was also revealed by the higher proportion of its iterations that reached the accuracy (46%) and precision (72%) scores in the top 10 percentile compared to other GMM-supervised algorithm based classifiers **(Figure 4)**. While the recall scores were similar for all GMM-supervised algorithm combinations, the median ROC AUC score of 0.93 as well as 62% of the iterations reaching in the top 10 percentile for the GMM-ANN classifier was again higher than other GMM-supervised algorithm based classifers **(Table 2B)**. However, a direct comparison of the performance evaluation metrics for the addiction-like behavior for cocaine of the K median-ANN classifier to that of the GMM-ANN classifier revealed that the former was superior to the latter **(Figure 4)**.

Table 2A: Classifier based on K-median clustering followed by Supervised algorithm-based predictions for addiction-like behavior for cocaine

	Accuracy		Precision		Recall		ROC AUC score	
	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile
KNN	0.93	58%	0.93	72%	0.92	58%	0.92	58%
LR	0.92	56%	0.93	72%	0.91	52%	0.91	52%
SVM	0.93	60%	0.92	76%	0.93	60%	0.93	60%
ANN	**0.94**	**68%**	0.88	42%	**1**	**88%**	**0.94**	**64%**

Table 2B: Classifier based on GMM clustering followed by Supervised algorithm-based predictions for addiction-like behavior for cocaine

	Accuracy		Precision		Recall		ROC AUC score	
	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile
KNN	0.67	16%	0.75	28%	0.88	48%	0.88	48%
LR	0.73	6%	0.67	22%	0.87	46%	0.87	46%
SVM	0.68	10%	0.66	22%	0.89	48%	0.89	48%
ANN	**0.89**	**46%**	**1**	**72%**	0.60	28%	**0.93**	**62%**

GMM: Gaussian mixture model, SML: Supervised Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks

For alcohol, the K mean-ANN-based classifier (**Supplementary data: Kmean_alcohol.py**) resulted in higher median accuracy (0.96), precision (1), recall (0.95) and ROC AUC score (0.97) than the other K mean-supervised algorithm-based classifiers (**Figure 5**) (**Table 3A**). This classifiers superiority was also revealed in the higher proportion of iterations to reach the

accuracy (78%), precision (84%) and ROC AUC score (84%) in the top 10 percentile compared to other K mean-supervised algorithm-based classifiers. The GMM-ANN based classifier (**Supplementary data: GMM_alcohol.py**) resulted in higher median accuracy (0.9), precision (0.9) and ROC AUC score (0.91) than the alternatives. The superiority of this classifier was further supported by the higher proportion of its iterations that reached accuracy (46%), precision (48%) and ROC AUC score (52%) in the top 10 percentile as compared to other GMM-supervised algorithm-based classifiers (**Figure 5**) (**Table 3B**). However, a direct comparison of the performance evaluation metrics for the addiction-like behavior for alcohol of the K mean-ANN classifier to that of the GMM-ANN classifier revealed that the former was overall better than the latter (**Figure 5**).

Table 3A: Classifier based on K-mean clustering followed by Supervised algorithm-based predictions for addiction-like behavior for alcohol

	Accuracy		Precision		Recall		ROC AUC score	
	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile
KNN	0.92	66%	0.93	68%	0.94	78%	0.94	78%
LR	0.93	62%	0.93	68%	0.94	72%	0.94	72%
SVM	0.93	62%	0.93	68%	0.93	76%	0.93	76%
ANN	**0.96**	**78%**	**1**	**84%**	0.95	58%	**0.97**	**84%**

Table 3B: Classifier based on GMM clustering followed by Supervised algorithm-based predictions for addiction-like behavior for alcohol

	Accuracy		Precision		Recall		ROC AUC score	
	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile	Median	Scores in top 10 percentile
KNN	0.87	40%	0.90	50%	0.89	48%	0.89	48%
LR	0.87	42%	0.89	46%	0.89	46%	0.89	46%
SVM	0.86	40%	0.88	46%	0.89	44%	0.89	44%
ANN	**0.9**	**46%**	**0.90**	**48%**	0.86	44%	**0.91**	**52%**

GMM: Gaussian mixture model, SML: Supervised Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks

Together these results demonstrate that a classifier based on K-median/mean-ANN provides an unprecedented tool accurately to predict whether a single rat is vulnerable or resilient as assessed in a multisymptomatic model of addiction with great heuristic value with regards to the clinical definition of SUD **(Figure 6)**.

To cross-validate the classifier, the entire datasets related to cocaine and alcohol addiction-like behavior (n=88, n=150, respectively) were subjected to the K-median (**Supplementary data: All_cocaine_Kmedian.py**) / K-mean clustering (**Supplementary data: All_alcohol_Kmean.py**). All the rats originally characterized as 0 or 3crit in their respective cohort were correctly labelled as Resilient or Vulnerable, respectively, revealing an absolute

intersection (**Table 4**) (**Supplementary data: Cocaine_crit_correspondence.xlsx, Alcohol_crit_correspondence.xlsx**).

Table 4A: Addiction-like behavior for cocaine

	0Crit in the original cohort	3Crit in the original cohort
Resilient (K median clustering)	36	0
Vulnerable (K median clustering)	0	15

Table 4B: Addiction-like behavior for alcohol

	0Crit in the original cohort	3Crit in the original cohort
Resilient (K mean clustering)	64	0
Vulnerable (K mean clustering)	0	18

Discussion:

The next frontier in addiction research lies in the understanding of the environmental, psychological and biological mechanisms that mediate, in vulnerable individuals, the transition from controlled drug intake to the compulsive seeking and taking characteristic of SSUD. Behavioral procedures that enable the study, under controlled conditions, of individual trajectories from a drug naïve state to the development of addiction-like behavior, or not, over the course of drug self-administration (12, 14, 20, 22, 24, 27, 28) have only started to demonstrate their utility in our understanding of the brain mechanisms of the individual vulnerability to addiction. These procedures have hitherto been limited by a lack of objective diagnosis strategy that is not influenced by the physical properties of the cohort to which a single individual belongs. This results in the unwarranted need to train large cohorts of animals at any given time and detracts the approach from the individual-centered diagnosis in humans.

In this study we drew on large datasets produced over the past decade to develop a new machine-learning assisted classifiers for cocaine or alcohol addiction-like behaviour that characterizes with 100% accuracy single individuals, irrespective of the cohort to which they belong, as resilient or vulnerable.

The optimal classifier relied on Artificial Neural Networks combined with antecedent K-median or /K-mean clustering, for cocaine and alcohol, respectively.

The role of clustering algorithms is to identify data-points in a multidimensional space that are closer to one another than they are to any other data point in the cloud (43). In many real-life situations the labels of such data-points are obvious, e.g., Males vs Females for biological differences, Democrat vs Republican or voted for or against Brexit. In these situations,

clustering the data is not necessary. However, ascribing labels, such as those necessary for determining if an individual meets the criteria for a diagnosis of addiction, cannot be informed by a natural dichotomic segregation of the population. This requires to structure a multidimensional space in specific delineated sub-spaces, or clusters, which can be used to ascribe a specific label to each individual constituent of the cluster and to train supervised classification algorithms in order to successfully predict the label, or, in other words, the specific cluster to which they most likely belong of a single individual whose data have never been used to train the classification algorithm.

The first step for the development of such algorithm was to objectively determine the number of clusters that should be used to structure the multidimensional cloud in a way that accommodates the physical properties of the data and the objective of the classifier. In real life, individuals can be categorized as being vulnerable or resilient to the development of SUD, thereby suggesting that any experimental population could be segregated into two clusters (10, 37, 38). Nevertheless, a data-driven approach was carried out to ensure that such dichotomy was actually present in the experimental datasets. The Silhouette algorithm ran on all the datasets used in the present study systematically revealed that the multidimensional space of the datasets was predominantly structured around two clusters, an outcome that is compatible with the prerequisite of the algorithm: to segregate two subpopulations from heterogenous groups, namely vulnerable and resilient individuals.

The objective identification of a two-cluster based structure of the multidimensional space provides an unbiased threshold for the various cluster analyses (GMM and K-median/K-mean) used in the several potential classifiers tested in this study.

The identification of resilient or “addicted” rats in the 3-Criteria model has hitherto been based on the application of a bimodal distribution of each population for resistance to punishment (12, 20, 27) which comprises a large log-normally distributed subpopulation of non-compulsive rats (60 to 70% of the population) tailed by an independent, normally distributed population of compulsive rats (30 to 40% of the population). Since GMM clustering algorithms can fit bi/multimodal distributions of data (44), it was originally used to assimilate such physical property on which depends the selection threshold for addiction-like behaviour. However, the GMM-based classifier did not yield outputs with as good an accuracy as the K-median/K-mean based classifier. This surprising outcome can be due to the fact that a GMM classifier, in contrast with the strategy we developed to apply the 30-40% threshold to the other two criteria, each characterized by a log-normal distribution, uses differential densities across quartiles in each variable independently to develop the classifier. Additionally, it may be due to the difference in the nature of the data fed to the classifier as compared to those classically used

to establish the addicted phenotype in the 3-Criteria model of cocaine addiction. The model has hitherto used namely a resistance to punishment expressed as a percentage baseline intake for compulsivity and last ratio completed in a progressive ratio test for motivation. In contrast, the classifier developed here was based on unidimensional variables (using the same unit), namely number of responses (lever presses or nose-pokes).

K-median/K-mean clustering, which is based on the Euclidean distance between the data-points in a three-dimensional vector space that plots a same response (number of responses) along three axes representing three different psychological constructs, was revealed to be the superior clustering method to accurately and consistently ascribe labels of resilience vs vulnerability. Not only are K-median/K-mean clustering algorithms easy to implement, but they are scalable (they can be applied to small or larger datasets) and they can be used to separate non-linearly separable data.

These properties were exploited to develop a robust and universal classifier. Thus, the same clustering algorithms were applied to fifty independent sets drawn from a large dataset comprising, in the case of cocaine addiction-like behavior, data from experiments carried out in different laboratories, on different strains (Sprague Dawley (14, 21) or Lister Hooded (20)) that differ in addiction relevant traits (45) and using different instrumental responses (nose-pokes (14, 21) or lever presses (20)). The ability of the classifier to survive randomization tests and to generalize across response modalities and strains demonstrates its potential use across a large repertoire of experimental idiosyncrasies that may reflect the behavioral heterogeneities observed by clinicians when a diagnosis is warranted.

Nevertheless, the same classifier could not be generalized from addiction-like behavior for one drug to another. Indeed, while the k-median clustering-based algorithm used for addiction-like behavior for cocaine systematically yielded the right vulnerability/resilient labels, even when applied to a dataset never used in its development, it was sub-optimal in the case of addiction-like behavior for alcohol, the best classifier for which was based on k-mean clustering. The lack of generalizability of a given classifier across drugs is considered here a further evidence of construct and predictive validity since AUD and SUD are considered to be independent diagnoses in humans and they have long been shown to involve different psychological and neurobiological mechanisms (46). In addition, while the 3-Criteria model for cocaine addiction relies on the assessment of compulsive cocaine intake (a consummatory response conflated with the preparatory response as it is the case under fixed ratio schedules of reinforcement) (11), the 3-Criteria model for AUD is based on the assessment of the compulsive nature of a seeking response in a chained schedule where lever pressing results in the procurement of alcohol, the ensuing consumption of which occurs in a dedicated

magazine, involving a set of behavioural responses independent of the instrumental component of the chain. Considering how neurally and psychologically dissociable preparatory and consummatory responses are (47, 48), it was not expected that a single classifier could be used across measures of compulsive taking and compulsive seeking. However, it will be interesting to test in future studies if the AUD-specific K-mean-ANN-based classifier can be applied to compulsive cocaine seeking data, as measured in seeking-taking heterogenous chained schedules of reinforcement, which dissociated physically and spatially seeking response from taking/consummatory responses for intravenously administered drug (49, 50).

Irrespective of the outcomes of these future studies, a one-fit-all approach does not seem to be an optimal expectation. One important avenue for future research is to identify further mathematical tools that will enable the introduction of dimensionality within the categories that are now identified accurately with the K-mean/K-median-ANN based classifiers. The 3-Criteria model was designed to have construct validity with regards to the diagnosis strategy, as defined in the DSM-IV (13), e.g., prior to the development of the RDoC (51). Nevertheless, the approach we had then developed embedded a dimensional aspect, in that rats were not only stratified as showing 0 criterion or 3 criteria (and were deemed resilient and showing addiction-like behavior, respectively), but 30% to 40% of any population was also stratified as showing 1 or 2 criteria, with 1crit and 2 crit rats being considered similar to 0crit and 3crit respectively (52, 53).

Since all the resilient rats identified by our classifier included 0crit and most of the 1 crit rats, and no 3crit rat, whereas all the rats identified as vulnerable included 3crit and most of the 2crit rats but no 0crit rat, it can be suggested that the present classifier does not yet provide the dimensional granularity necessary to distinguish several levels of severity (2crit vs 3crit) within the vulnerable population (**Supplementary data: Cocaine_crit_correspondence.xlsx, Alcohol_crit_correspondence.xlsx**). Future research is warranted to determine whether the addition of biological endophenotypes (20, 21, 27, 28) to our classifiers will enable them fully to comply with the dimensional nature of the debilitating condition that is SUD.

Conclusion:

The present machine learning based classifiers represent a unique tool objectively to identify whether a single experimental subject is resilient or vulnerable to SUD for cocaine or alcohol (**Figure 6**). The ability conferred by such a tool to consider a single individual irrespective of the experimental cohort to which it belongs (and the associated experimental conditions) bridges a new frontier in the study of the individual vulnerability to develop SUD, bringing the

focus back on the individual, as it is the case in humans. It can be boldly envisioned that, with the advent of large data sets in humans from imaging, genomics and proteomic approaches a successful back-translation strategy could see the application of such machine learning-assisted tools to a personalized diagnosis of clinical populations.

Conflict of Interest:

The authors declare no competing financial interests.

Acknowledgements:

Funding

DB is supported by a Programme Grant from the Medical Research Council to Barry Everitt, DB, Amy Milton, Jeffrey Dalley and Trevor Robbins (MR/N02530X/1). VDG was supported by ANR-13-NEUR-0002-01 (ERA-NET NEURON II), ANR-10-LABX-43 (LABEX BRAIN), ANR-10-EQX-008-1 (EquipEx OptoPath™), INSERM and Université de Bordeaux. BB is supported by a Swiss National Science Foundation grant (310030_185192)

KSJ is the recipient of the Swiss Government Excellence Fellowship (2015-2018), Doc mobility Fellowship (2018-2019) and Early Post Doc mobility Fellowship (2021-2022) from the Swiss National Science Foundation.

Author contribution

KSJ developed the algorithms and wrote the codes. BBJ provided substantial technical inputs for the code. KSJ, DB, VDG and BB wrote the manuscript

Acknowledgement for assistance

BB and KSJ would like to thank Dr Ivana Arsic, (Data Scientist, Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Switzerland) for her inputs on the algorithm.

KSJ would like to thank Mr. Dhaval Joshi, PhD student in the Belin lab for critical insights that helped to refine the algorithms and the annotating the code in the .py files.

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Figure Legends:

Figure 1: Individual trajectories in the development of substance use disorder: A translational perspective

Individuals who consume drugs, inadvertently take a risk since 10-40% of them eventually develop substance use disorder. While the majority maintain control over drug use, only a small proportion of individuals (humans/rats) progress to develop compulsive drug seeking which characterizes addiction. Recreational users will display drug-induced neurobiological changes (displayed here in green), but these changes, identified when recreational users are compared with drug naïve controls for instance, are not reflective of the adaptations to drug exposure that take place in the brain of vulnerable individuals (displayed here in pink), and which eventually mediate the transition to SUD and the associated high tendency to relapse. A frontier in addiction research is to understand what these addiction-specific adaptations are and what makes the brain of a vulnerable individual vulnerable. Over the past decades, it has been shown that similar differences exist in the tendency to develop addiction-like behaviour in rodents exposed to drug self-administration, and associated mechanisms identified in prospective longitudinal studies in rodents have systematically been verified in humans.

Figure 2: Workflow of the Machine Learning classifier

The steps are illustrated as numbers in the circles. Clustering algorithms used are Gaussian Mixture Method and K-mean/ K-median Clustering. Classification algorithms used are K nearest neighbor, Logistic Regression, Support Vector Machines and Artificial Neural Networks. The blue arrows indicate the clustering algorithms and the green arrows indicate the classification algorithms

Figure 3: Illustration of an Artificial Neural Network

The hidden layer consists of neurons with the ELU (Exponential Linear Unit) activation function. Feed forward network entails multiple forward passes through the hidden layers. One forward pass consists of consecutive matrix multiplications at each layer by utilizing random weights to initialize the training which are then adjusted during backpropagation to minimize the cross entropy loss function.

Figure 4: Performance evaluation metrics of the Machine Learning classifier of the Addiction-like behavior for cocaine in rats

Figure 4A-4D depict the Accuracy, Precision, Recall and ROC AUC score respectively of the GMM clustering based classifier followed by four Supervised Machine Learning algorithms. Figure 4E-4H depict the Accuracy, Precision, Recall and ROC AUC score respectively of the K-median clustering-based classifier followed by the four Supervised Machine Learning algorithms.

GMM: Gaussian Mixture Method, ML: Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks

Figure 5: Performance evaluation metrics of the Machine Learning classifier of the Addiction-like behavior for alcohol in rats

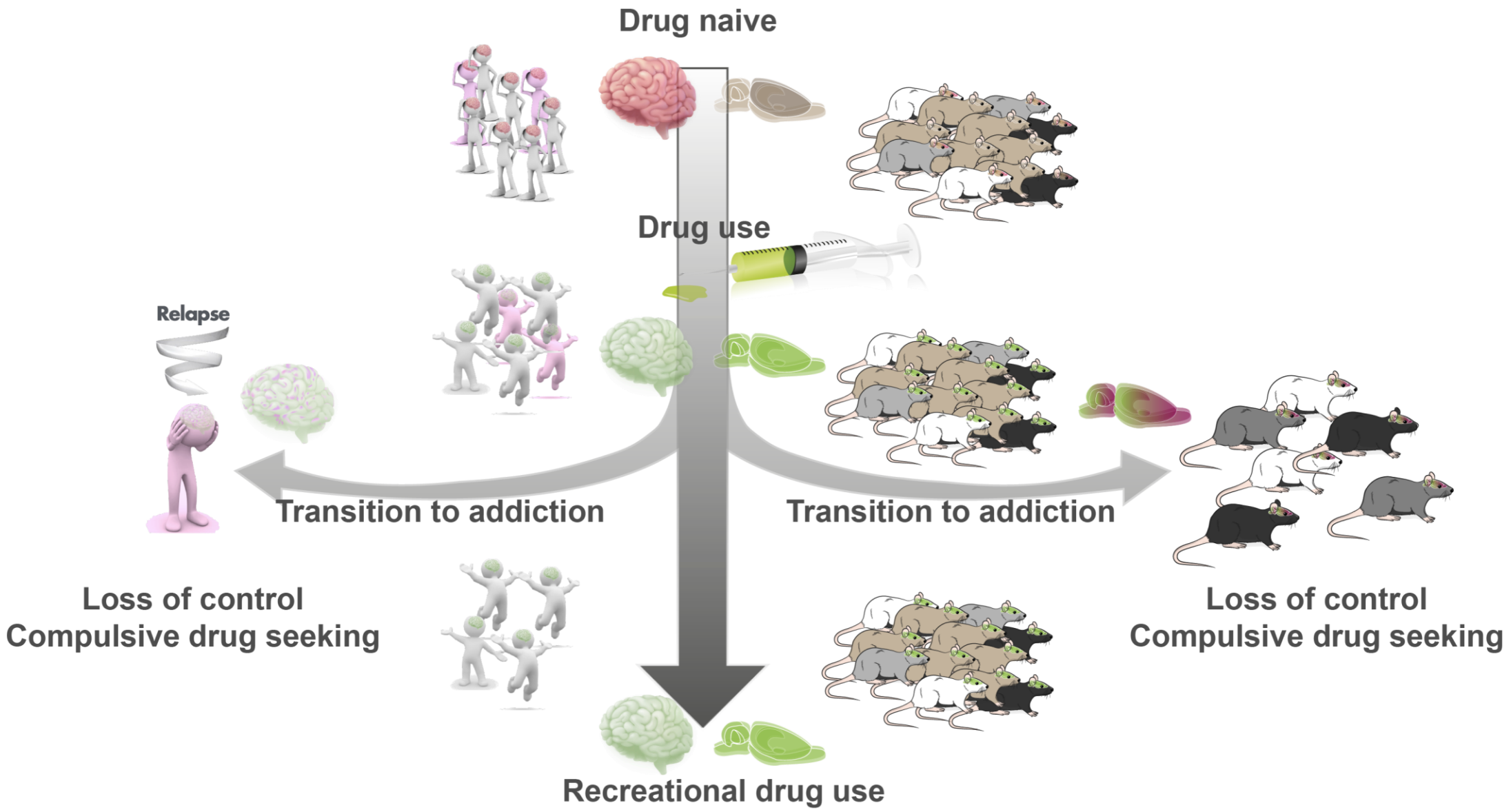
Figure 5A-5D depict the Accuracy, Precision, Recall and ROC AUC score respectively of the GMM clustering based classifier followed by four Supervised Machine Learning algorithms. Figure 5E-5H depict the Accuracy, Precision, Recall and ROC AUC score respectively of the K-mean clustering-based classifier followed by four Supervised Machine Learning algorithms.

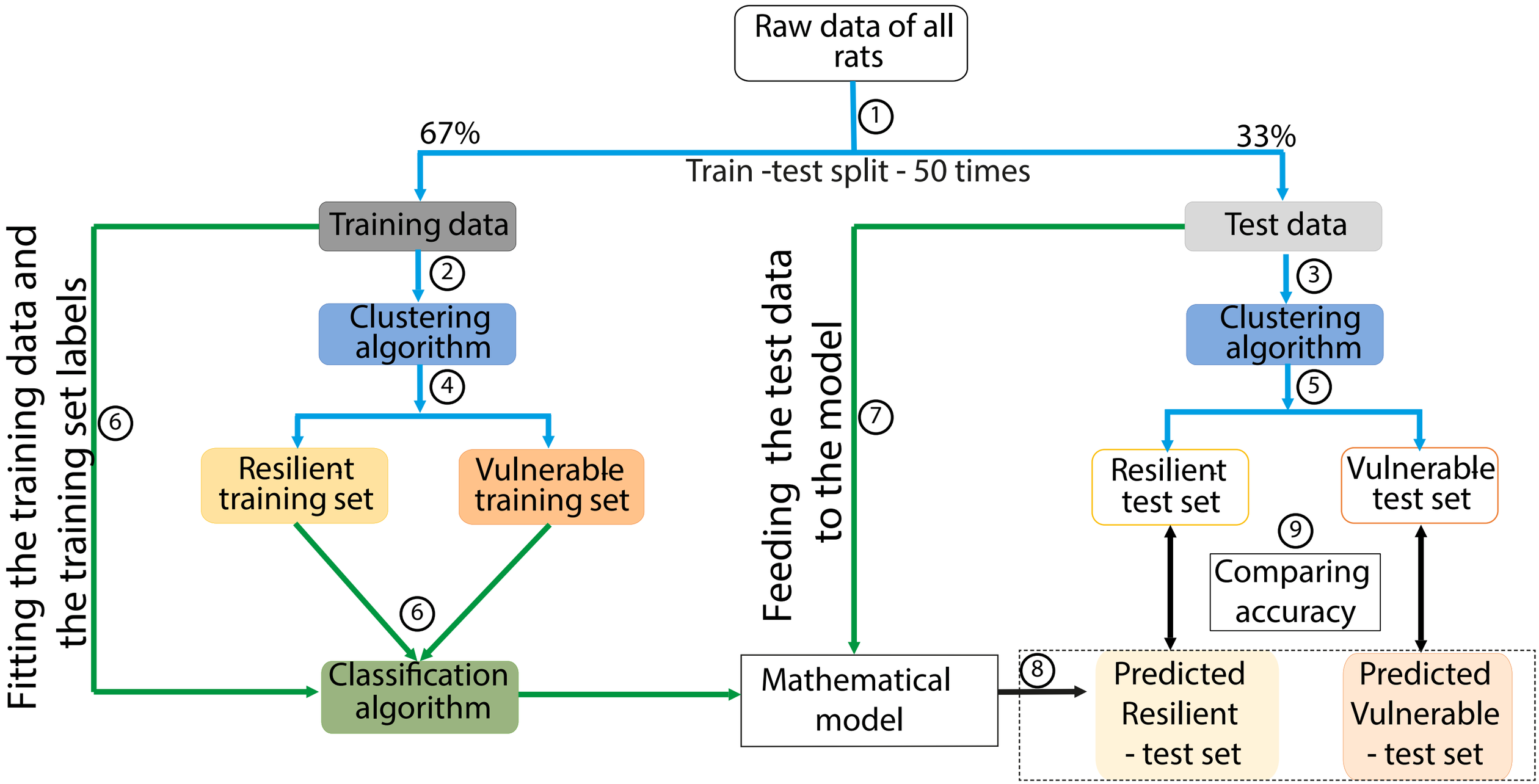
GMM: Gaussian Mixture Method, ML: Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks

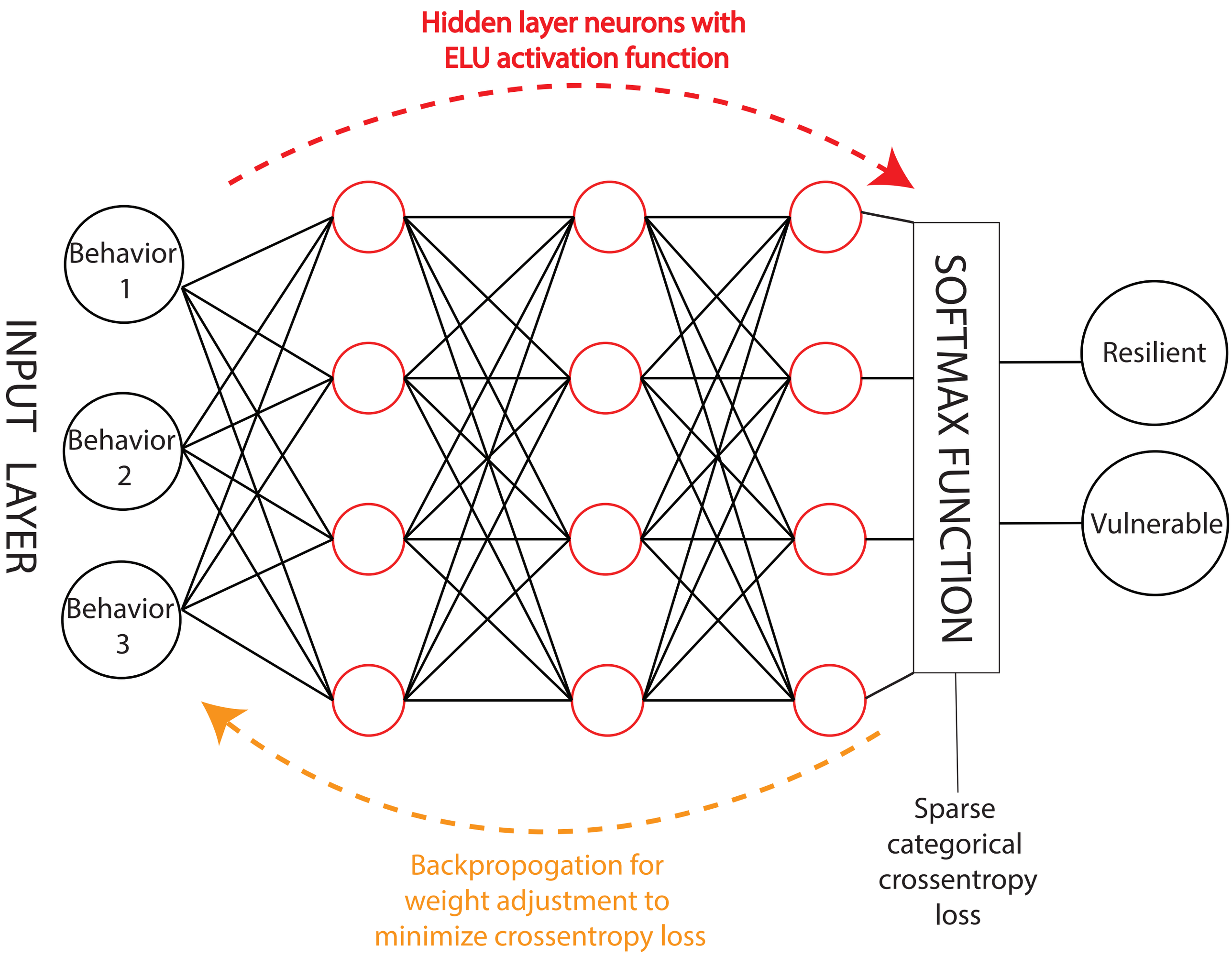
Figure 6: Flowchart of the classification of any future rat as resilient or vulnerable to SUD.

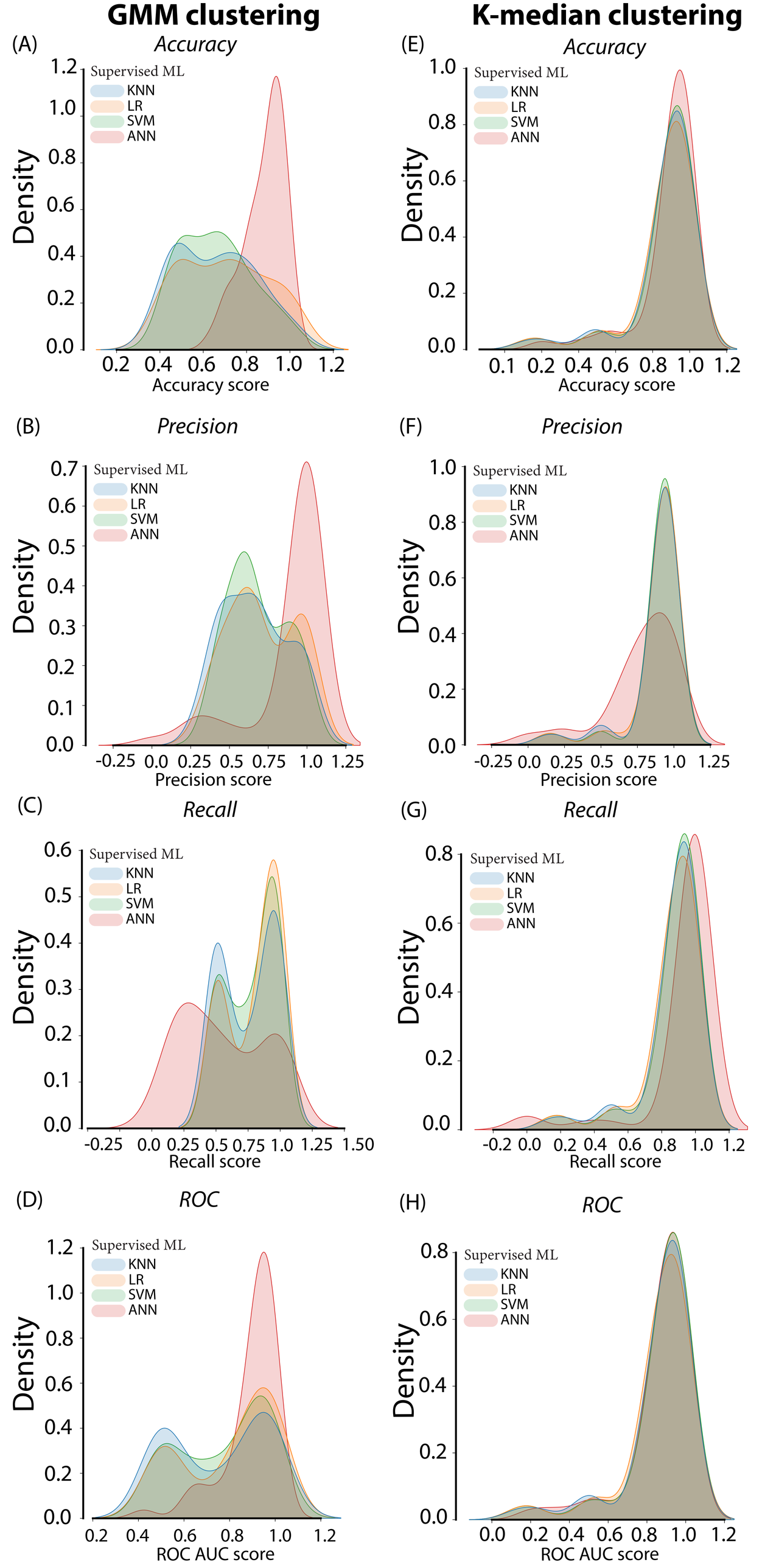
The steps are illustrated as numbers in the circles. Having established that the classifier based on K-median/K-mean clustering followed by ANN gives the best predictive accuracy, the addiction vulnerability status of a single rat irrespective of the cohort it is trained with. The blue arrows indicate the clustering algorithms and the green arrows indicate the classification algorithms

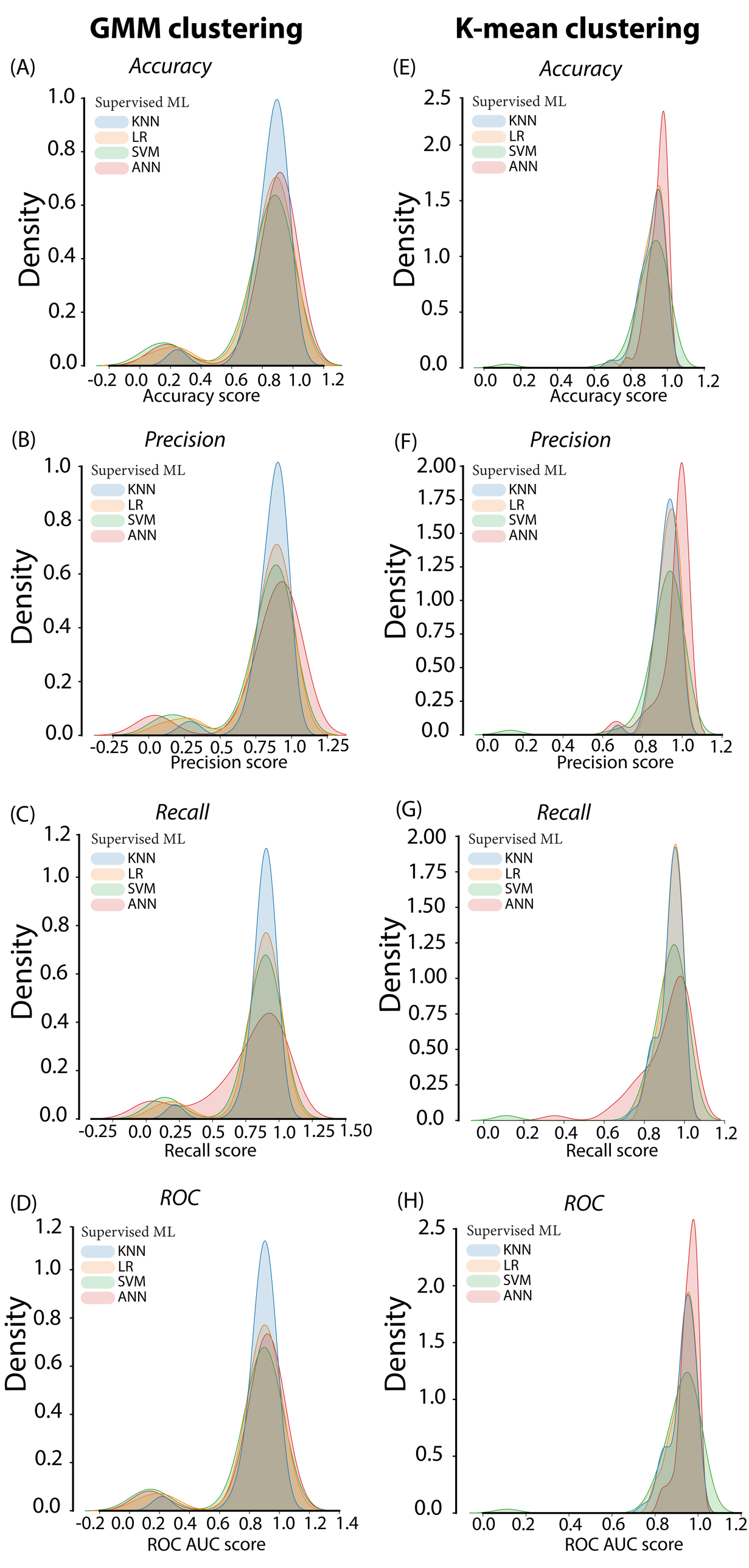
ANN: Artificial Neural Network

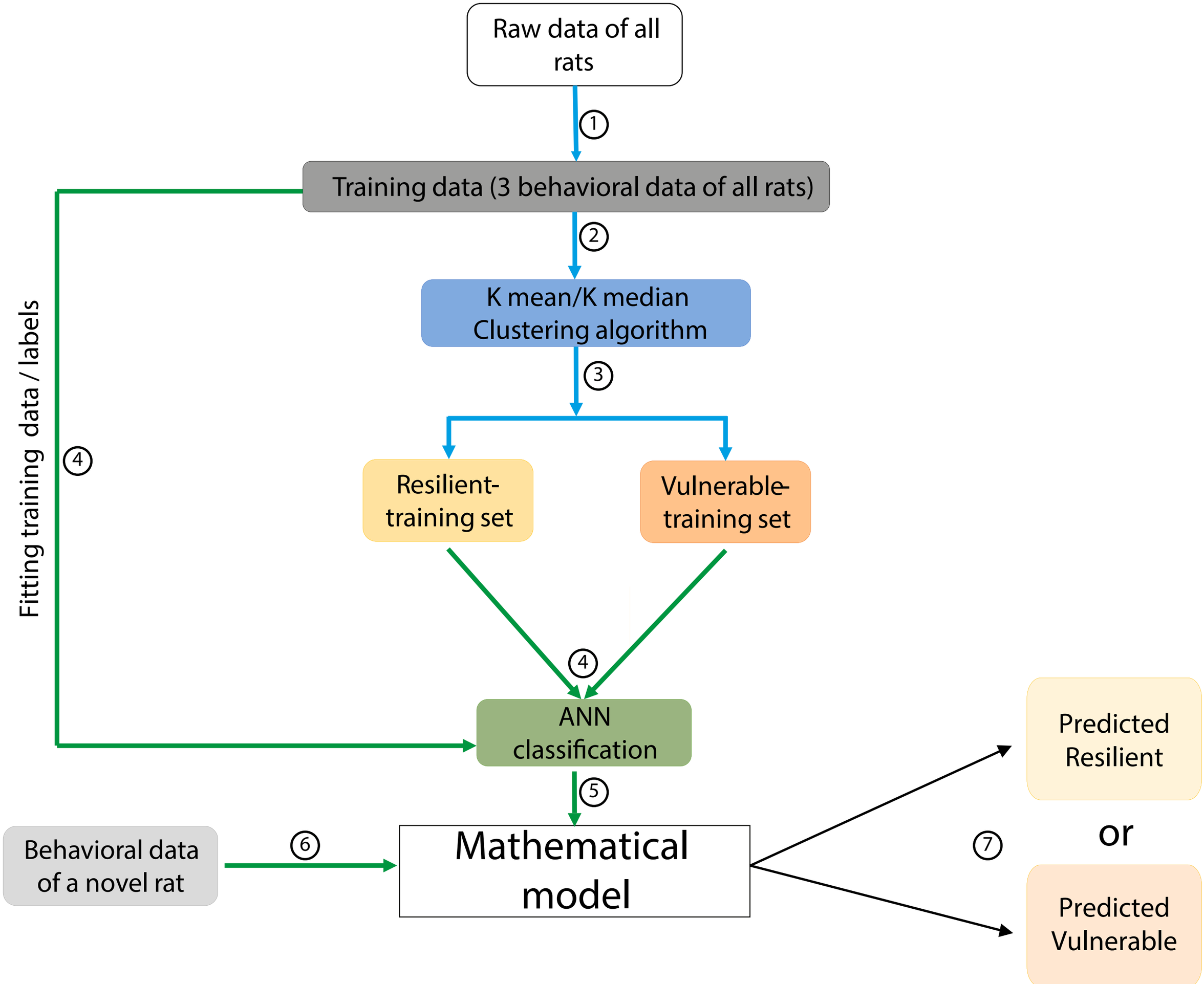

Drug naive
Drug use
Relapse
Transition to addiction
Transition to addiction
Loss of control
Compulsive drug seeking
Loss of control
Compulsive drug seeking
Recreational drug use


Raw data of all rats
1
67%
33%
Train -test split - 50 times
Training data
Test data
2
3
Clustering algorithm
Clustering algorithm
4
5
Resilient training set
Vulnerable training set
Resilient test set
Vulnerable test set
6
6
7
9
Comparing accuracy
Fitting the training data and the training set labels
Feeding the test data to the model
Classification algorithm
Mathematical model
8
Predicted Resilient - test set
Predicted Vulnerable - test set


Hidden layer neurons with
ELU activation function
INPUT LAYER
Behavior 1
Behavior 2
Behavior 3
SOFTMAX FUNCTION
Resilient
Vulnerable
Sparse categorical crossentropy loss
Backpropogation for weight adjustment to minimize crossentropy loss


GMM clustering
K-median clustering
(A)
Accuracy
Supervised ML
KNN
LR
SVM
ANN
Density
Accuracy score
(E)
Accuracy
Supervised ML
KNN
LR
SVM
ANN
Density
Accuracy score
(B)
Precision
Supervised ML
KNN
LR
SVM
ANN
Density
Precision score
(F)
Precision
Supervised ML
KNN
LR
SVM
ANN
Density
Precision score
(C)
Recall
Supervised ML
KNN
LR
SVM
ANN
Density
Recall score
(G)
Recall
Supervised ML
KNN
LR
SVM
ANN
Density
Recall score
(D)
ROC
Supervised ML
KNN
LR
SVM
ANN
Density
ROC AUC score
(H)
ROC
Supervised ML
KNN
LR
SVM
ANN
Density
ROC AUC score


GMM clustering
K-mean clustering
(A)
Accuracy
Supervised ML
KNN
LR
SVM
ANN
Density
Accuracy score
(E)
Accuracy
Supervised ML
KNN
LR
SVM
ANN
Density
Accuracy score
(B)
Precision
Supervised ML
KNN
LR
SVM
ANN
Density
Precision score
(F)
Precision
Supervised ML
KNN
LR
SVM
ANN
Density
Precision score
(C)
Recall
Supervised ML
KNN
LR
SVM
ANN
Density
Recall score
(G)
Recall
Supervised ML
KNN
LR
SVM
ANN
Density
Recall score
(D)
ROC
Supervised ML
KNN
LR
SVM
ANN
Density
ROC AUC score
(H)
ROC
Supervised ML
KNN
LR
SVM
ANN
Density
ROC AUC score


Raw data of all rats
1
Training data (3 behavioral data of all rats)
2
K mean/K median Clustering algorithm
3
Resilient-training set
Vulnerable-training set
4
ANN classification
5
Fitting training data / labels
4
Behavioral data of a novel rat
6
Mathematical model
7
Predicted Resilient
or
Predicted Vulnerable