Title:

Towards a machine-learning assisted diagnosis of psychiatric disorders and their operationalization in preclinical research: evidence from studies on addiction-like behaviour in individual rats

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Running title:

ML-based diagnostic tool for addiction-like behaviour

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Abstract:

Background: Over the last few decades there is a progressive transition from a categorical to a dimensional approach to psychiatric disorders. Especially in case of substance use disorders, the increased interest in the individual vulnerability to transition from controlled to compulsive drug seeking and taking warrants the development of novel dimension-based objective diagnostic or stratification tools. Here we drew on a multidimensional preclinical

model of addiction, namely the 3-criteria model, previously developed to identify the neurobehavioural basis of the individual vulnerability to switch from control to compulsive drug taking, to test the potential interest of a machine-learning assisted classifier objectively to identify individual subjects as vulnerable or resistant to addiction.

Methods: Large behavioural datasets from several of our previous studies on addiction-like behaviour for cocaine or alcohol were fed to a variety of machine-learning algorithms (each consisting of an unsupervised-clustering method combined with a supervised-prediction algorithm) 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 a highly reliable and accurate tool to predict if a single rat is vulnerable or resilient to addiction. Thus, each of the rats previously characterized as displaying 0 criterion (i.e., resilient) or 3 criteria (i.e., vulnerable) in individual cohorts were correctly labelled 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-like behaviour in rats. This novel dimension-based classifier thereby increases the heuristic value and generalizability of these preclinical models while providing proof of principle for the deployment of similar tools for the future of diagnosis of psychiatric disorders.

Introduction:

Background:

There is a progressive transition from a categorical to a dimensional approach to psychiatric disorders (1-4). Meanwhile, a growing interest in the preclinical field of substance use disorder (SUD) is emerging, acknowledging the biobehavioural basis of the individual tendency to display aberrant, persistent, or compulsive, drug seeking and/or taking (5-10), warrants the development of new dimension-based objective diagnostic or stratification tools aiming at unveiling dimension-based, trans-nosological endophenotypes of vulnerability to SUDs.

Indeed, like for many psychiatric disorders, the presence of a triggering factor, such as exposure to a drug in the case of SUD, is not sufficient for the development of the several behaviours, which by the extreme nature of their manifestation alongside the continuum of their respective dimension, are characteristic of the pathology. This individual vulnerability to transition from controlled, recreational drug use to the compulsive drug seeking and taking that characterizes SUD (**Figure 1**) has long been suggested to stem from the interaction between environmental, psychological, neurobiological and behavioural factors (11-18). However, it is difficult to identify and study the biobehavioural basis of the factors conferring this vulnerability in humans, not least because such endeavours require the study of large populations across the lifetime in controlled conditions, with little if any opportunity to carry out the invasive manipulations that are necessary causally to identify 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 behaviour (19). Indeed, as in humans, all individual rats who regularly self-administer or seek addictive drugs do not necessarily lose control over drug intake and develop the persistent, compulsive drug-seeking and taking that

characterizes substance use disorder (SUD) **(Figure-1)** (20). In this context, in the early 2000's a multidimensional model of addiction was developed (21) based on the intersectionality of specific behavioural characteristics that are the operationalization of DSM-IV criteria (22), namely, increased motivation to take the drug, inability to refrain from drug-seeking and maintained drug use despite aversive consequences. This approach enables the identification of divergent trajectories of the transition from controlled to compulsive drug intake (**Figure-1**), in that only ~20% of a given population of outbred rats exposed to cocaine will eventually display the three behavioural criteria following a prolonged (>60 daily sessions) history of self-administration. Importantly, rats identified as displaying the 3-Criteria for addictive-behaviours also show an increased tendency to escalate their drug intake when access is illimited, and they are prone to relapse following abstinence (23), thereby displaying additional behavioural manifestations reminiscent of diagnostic criteria for which they were not selected. The construct and predictive validity of the 3criteria model was further substantiated as these differences between vulnerable and resilient rats are not due to a differential cocaine exposure since all rats self-administer the same amount of drug before being identified as 3 vs 0 criteria (21). However, while they do not take more cocaine, 3crit rats develop a binge-like pattern of intake that precedes the transition to addiction (23).

The 3-Criteria model has led to several breakthroughs in our understanding of the vulnerability to addiction which together represent a unique success story of translational research. This model first helped establish that impulsivity (24) and boredom susceptibility (25) confer a vulnerability to switch from controlled to compulsive cocaine intake. In contrast, both sensation seeking, assessed as a greater locomotor response to novelty, and sign tracking, which predict an increased tendency to initiate drug self-administration and to respond to drug-paired cues, respectively, were revealed to confer resilience to addiction-like behaviours (24, 26). These observations in rats have paved the way for studies in humans confirming that the factors associated with recreational cocaine use are dissociable from those specifically associated with the transition to SUD (27). The evidence of a causal relationship between a

high impulsivity trait and the subsequent vulnerability to develop compulsive behaviours (24, 28) has far-reaching implications for our understanding of the neural basis of addiction (26, 29, 30) which the model helped reveal to be very different to the biological responses to drug exposure. Thus, the tendency to persist in drug taking despite adverse consequences is associated with a rigidity, not an exacerbation, as it is the case following single or repeated administrations of drugs, of drug-induced synaptic plasticity (31-33).

This multidimensional approach has since been applied to the study of the neural and psychological basis of the vulnerability to develop alcohol use disorder (AUD) (34, 35) or uncontrolled food seeking (36) illustrating the high translational value of novel preclinical models that encapsulate the multidimensional nature of SUD and the importance of focusing on the individual.

However, these procedures are all dependent on defining a threshold above which a behaviour is deemed maladaptive, but where the cursor should be placed on a continuum to consider a behaviour abnormal is a very challenging question, especially at a time of a transition from categorical to dimensional approaches. For example, in the 3-Criteria model, the threshold used for the scoring of each addiction-like criterion is determined by the physical properties of the distribution of the population for one of the three criteria, namely resistance to punishment (21, 24, 25, 37). The bimodal distribution of this dimension offers an objective threshold selection for the associated criterion, but its application to the two other criteria, inability to relinquish drug seeking even in the absence of the drug and high motivation for the drug, which both follow a log-normal distribution, relies on the assumption that a similar rupture in the continuum exists in them too, which is an inherent limitation. In addition, a distribution-based threshold selection to ascribe diagnostic scores puts too large an emphasis on the population to which each individual belongs, the physical properties of which eventually contributing almost as much as the individual characteristics themselves to its characterization as displaying addiction-like behaviour or resilience to addiction. This thereby precludes the determination of the vulnerability status of a given individual considered independently of a

particular cohort, a limitation of the underlying approach which together with the associated need to train large cohorts at once for long periods of time may have hindered the widespread adoption of the 3-criteria model.

Recent developments in machine learning may offer unprecedented means to overcome the aforementioned limitations as they have been suggested to refine the classification of individuals, including psychiatric patients, within sub-groups with shared underlying endophenotypes, to tailor treatment strategies (38). These approaches also have an advantage over classical statistics (e.g. null hypothesis testing, ANOVAs), since they uncover substructures/subgroups in data without necessarily receiving specific instructions. Further, the models built using machine learning tools can also extrapolate patterns learnt from the data with which they are trained to entirely new data sets with individual precision.

Hence, here we used the 3-Criteria multidimensional models for cocaine or alcohol addiction, to test the potential of machine-learning assisted classifiers to identify individuals with or without addiction-like behaviour in drawing on diagnostic-relevant dimensions of addiction (20, 22). For this we subjected the individual scores in each of the three addiction-like behaviors to different clustering algorithms and then validated the labels using supervised prediction algorithms.

Materials and Methods:

Data:

For addiction-like behaviour for cocaine, data from 3 published papers (23-25) were pooled, representing a cohort of 88 individuals **(All_data_cocaine.csv)**. For addiction-like behaviour for alcohol, the data were pooled from 2 published (34, 35) and 1 unpublished experiment with a cohort of 150 rats **(All_data_alcohol.csv)**.

All analyses were processed using Python 3.8 using Numpy, Pandas and Scikit-learn packages as well as TensorFlow-Keras for deep learning methods (39, 40).

The active lever presses performed in each of the three behaviours (termed as raw data), namely, increased motivation to take the drug, inability to refrain from drug seeking and maintained drug use despite aversive consequences (compulsivity), were used as the three dimensions, injected in the algorithms.

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

Algorithm:

Individuals consuming drugs can be categorized as resilient or vulnerable to the development of SUD, the latter further being distributing along a clinical continuum of severity (18, 41, 42), suggesting that any population could be segregated in two clusters. Nevertheless, the optimal cluster number 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 to inform the expected cluster number based on the actual experimental dataset **(cluster_number_cocaine.py, cluster_number_alcohol.py)** and the one most commonly informed by the Silhouette algorithm across 100 iterations, was included as an input in the clustering algorithms of the classifiers tested in the study.

Behavioural data of a single pair of TRAINING and TEST set was subjected to Unsupervised-Clustering algorithms **(Figure-2②,③)** (namely Gaussian Mixture Model (GMM) (43) or K-mean/K-median clustering (44)) **(SOM)** to determine resilient and vulnerable rats in both sets **(Figure-2④,⑤)**.

We used four Supervised Classification algorithms **(SOM),** namely K nearest neighbour (KNN) (44), Logistic Regression (LR) (45), Support Vector Machines (SVM) (39) and Artificial Neural Networks (ANN) (46) (**Figure-3**) to fit the behavioural data of the TRAINING SET and the

labels assigned by the clustering algorithm to generate a mathematical model that best explains the behavioural data and the labels of the rats in the TRAINING SET **(Figure-2⑥)**.

For ANN, increasing numbers of hidden layers were used (5, 50 and 500), keeping the number of neurons in each layer constant, to test both a potential tendency to overfitting and the ability of the algorithm to accommodate larger sample sizes in the future. Then, to predict the labels of the rats belonging to the TEST set, their behavioural data were submitted to the mathematical model **(Figure-2⑦)** generated by each of the four Supervised Classification algorithms.

When submitted to these mathematical model, the behavioural data of the TEST SET are used to ascribe a resilient or vulnerable label to each rat of the TEST SET **(Figure-2⑧)** (39). Thus, each 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)**.

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

Accuracy ([TV+TR]/[TV+TR+FV+FR]), precision(TV/[TV+FV]), recall (TV/[TV+FR]) and ROC AUC (47) scores were calculated from the classification matrix (**SOM**).

Each pair of TRAINING and TEST SET were subjected to this pipeline four times, i.e. GMM-clustering 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 four supervised prediction algorithms.

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 behaviour for cocaine, Silhouette score revealed 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 behaviour for alcohol, 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 3-6. This analysis confirmed that 2 clusters should be used in subsequent analyses.

For addiction-like behaviour for cocaine, Kmedian-KNN, Kmedian-LR and Kmedian-SVM (**Kmedian_cocaine.py**) classifiers yielded similar scores (**Table 2A, Figure 4**) that were overall superior to GMM-KNN, GMM-LR and GMM-SVM (**GMM_cocaine.py**) classifiers with regard to median accuracy, precision, recall and ROC-AUC scores as well as the proportion of iterations reaching the top 10 percentile, respectively (**Table 2, Figure 4**). The Kmedian-ANN classifier and GMM-ANN classifier gave similar median accuracy and ROC-AUC scores and resulted in a similar proportion of these scores being in the top 10 percentile (**Table 2, Figure 4**).

For addiction-like behaviour for alcohol, Kmean-KNN, Kmean-LR, Kmean-SVM and Kmean-ANN classifiers yielded similar scores for all the performance evaluation metrics (**Table 3A, Figure 5**) that were overall superior to those obtained by GMM-KNN, GMM-LR, GMM-SVM and GMM-ANN classifiers (**Table 3, Figure 5**).

The performance of the Kmedian- and GMM-ANN or Kmean- and GMM-ANN classifiers was further improved by an increase in the number of hidden layer neurons used in the ANN (**Table 2 and 3**). The ensuing increase in accuracy thereby demonstrates the ability of the Kmedian/Kmean-ANN classifiers to accommodate larger sample sizes and/or more dimensions, a feature that is not reflective simply of overfitting because of the back propagation and early stopping processes included in the ANN (48).

Together these results demonstrate that a classifier based on K-median/K-mean followed by ANN is the most robust and future- and dimension expansion-proof approach accurately to predict whether a single rat is vulnerable or resilient as assessed in our multisymptomatic model 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 behaviour (n=88, n=150, respectively) were subjected to the K-median (**All_cocaine_Kmedian.py**)/K-mean clustering (**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**) (**Cocaine_crit_correspondence.xlsx,Alcohol_crit_correspondence.xlsx**).

Finally, in order to establish the predictive potential of the classifiers we developed, we applied them to a completely new dataset (26) that consists of the 3criteria behavioural scores of a cohort of 36 rats housed either in a standard (2 individuals in a standard cage), or an enriched environment. While replicating previous findings that an environmental enrichment decreases the tendency to self-administer cocaine (49, 50), this study demonstrated that rats housed in an enriched environment were more vulnerable to develop addiction-like behaviour than rats raised in a standard environment (26) in that all the 3crit rats identified in this heterogeneous cohort came from the former. In line with the original study, none of the rats from the standard housing group were labelled as vulnerable by the classifiers, while those identified as vulnerable overlapped with 100% accuracy with those identified as 3crit that came from the enriched environment (**EEES.xlsx**) (26).

Discussion:

The next frontier in addiction research lies in understanding 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 SUD. Behavioural procedures that enable the study, under controlled conditions, of individual trajectories from a drug naïve state to addiction-like behaviour development, over the course of drug self-administration (21, 23, 24, 26, 29, 34, 35) have only started to demonstrate their utility in our understanding of the 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 data-distribution 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-centred diagnosis in humans.

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

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 (51). In many real-life situations, the labels of such data-points are obvious, e.g., Males vs Females for biological differences, or voted for or against Brexit. In these situations, data clustering is not necessary. However, ascribing labels, such as those to determine if an individual meets the criteria of addiction-like behaviour, cannot be informed by a natural dichotomic population segregation. This requires to structure a multidimensional space in delineated sub-spaces 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, i.e., 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 of such an algorithm development was to objectively determine the cluster number to structure the multidimensional cloud to accommodate the physical properties of the data and the objective of the classifier. In real life, individuals can be categorized as vulnerable or resilient, thereby suggesting that any experimental population could be segregated into two clusters (18, 41, 42). Nevertheless, a data-driven approach was used to ensure that such dichotomy was present in the experimental datasets. The Silhouette algorithm ran on all the datasets used here 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 heterogeneous groups, namely vulnerable and resilient individuals. This also provided an unbiased threshold for the various cluster analyses (GMM and K-median/K-mean) used in the several potential classifiers tested in this study.

Identification of resilient or vulnerable rats in the 3-Criteria model was hitherto based on the bimodal distribution of each population for resistance to punishment (21, 24, 34) which comprises a large log-normally distributed subpopulation of non-compulsive rats (60-70% population) tailed by an independent, normally distributed population of compulsive rats (30-40% population). Since GMM-clustering can fit bi/multimodal data distributions (52), 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 superior to 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.

K-median/K-mean clustering, which is based on the Euclidean distance between the data-points in a three-dimensional vector space that plots the 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 algorithms easy to implement, but they are scalable and 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 behaviour, data from experiments carried out in different laboratories, on different strains (Sprague-Dawley (23, 25) or Lister-Hooded (24) or Wistar rats (34, 35)) that differ in addiction relevant traits (53) and using different instrumental responses (nose-pokes (23, 25) or lever presses (24)). 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 behavioural heterogeneities observed by clinicians when a diagnosis is warranted. Further, the ability of the Kmedian/Kmean-supervised algorithm classifiers to accurately identify rats as being vulnerable to addiction or resilient from a completely different dataset generated with a heterogeneous cohort exposed to very different housing conditions to those used in the experiments used for the training datasets indicates that these tools can be deployed across many experimental conditions.

Nevertheless, the same classifier could not be generalized from addiction-like behaviour for one drug to another. While K-median clustering-based algorithm used for addiction-like behaviour for cocaine systematically yielded the right vulnerability/resilient labels, even when applied to a dataset never used in its development (the enriched environment experiment (26)), it was sub-optimal in the case of addiction-like behaviour for alcohol, the best classifier for which was based on K-mean clustering. The lack of generalizability of a given classifier across drugs is a further evidence of construct and predictive validity since AUD and SUD are independent diagnoses in humans and they have long been shown to involve different psychological and neurobiological mechanisms (54). In addition, while the 3-Criteria model for cocaine relies on the assessment of compulsive cocaine intake (consummatory conflated with preparatory responses as it is the case under fixed-ratio schedules of reinforcement) (19), the

3-Criteria model for alcohol 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 (55, 56), it was not expected that a single classifier could be used across measures of compulsive taking and seeking. However, it will be interesting to test in future studies if the alcohol-specific K-mean classifier can be applied to compulsive cocaine seeking data, as measured in seeking-taking heterogeneous chained schedules of reinforcement, which dissociated physically and spatially, seeking response from taking/consummatory responses for intravenously administered drug (57, 58).

Irrespective of the outcomes of these future studies, a one-fit-all approach is not an optimal expectation. One important avenue for future research is to identify mathematical tools that will enable the introduction of dimensionality within the categories that are now identified accurately with the K-mean/K-median classifiers. The 3-Criteria model was designed to have construct validity with regards to the diagnosis strategy of DSM-IV (22), i.e., prior to the development of the RDoC (1). 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 (deemed resilient and showing addiction-like behaviour, respectively), but 30-40% of any population was also stratified as showing 1 or 2 criteria, with 1crit and 2crit rats being considered similar to 0crit and 3crit respectively (34, 59, 60).

Since all the resilient rats identified by our classifier included 0crit, most of the 1crit and no 3crit rats, whereas all the rats identified as vulnerable included 3crit and most of the 2crit but no 0crit rats (**Cocaine_crit_correspondence.xlsx,Alcohol_crit_correspondence.xlsx**), 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 warranting further research to determine whether the addition of endophenotypes

(24, 25, 34, 35) to our classifiers will enable them to fully comply with the dimensional nature of the debilitating condition that is SUD. This could contribute to the several initiatives to identify clinically relevant subtypes of SUD (61) through cluster analysis of patients to better capture the clinical heterogeneity (62-66) with the aim to advance personalized medicine (67, 68).

Conclusion:

The present machine learning-based classifiers represent a unique tool to objectively identify whether a single experimental subject is resilient or vulnerable for cocaine or alcohol addiction-like behaviour (**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.

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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

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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)

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^5	0.86	26%	0.7	18%	1	72%	0.83	26%
ANN^{50}	0.93	52%	0.80	36%	1	88%	0.9	48%
ANN^{500}	0.96	48%	0.9	42%	1	92%	0.95	68%

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^5	0.9	34%	1	52%	0.36	22%	0.84	42%
ANN^{50}	0.93	60%	1	74%	0.67	38%	0.94	62%
ANN^{500}	0.93	56%	1	80%	0.6	24%	0.96	74%

GMM: Gaussian mixture model, SML: Supervised Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks. ANN^5, ANN^{50}, ANN^{500}: numbers indicate the number of hidden layers of the ANN

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^{5}	0.92	60%	0.93	60%	0.94	60%	0.93	66%
ANN^{50}	0.96	76%	1	74%	0.94	60%	0.96	88%
ANN^{500}	0.96	82%	1	86%	0.97	64%	0.97	90%

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^{5}	0.87	40%	0.88	46%	0.85	32%	0.89	46%
ANN^{50}	0.88	36%	0.91	56%	0.82	38%	0.89	44%
ANN^{500}	0.92	54%	0.91	64%	0.9	50%	0.92	60%

GMM: Gaussian mixture model, SML: Supervised Machine Learning, KNN: K nearest neighbor, LR: Logistic Regression, SVM: Support Vector Machines, ANN: Artificial Neural Networks. ANN^{5}, ANN^{50}, ANN^{500}: numbers indicate the number of hidden layers of the ANN

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

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

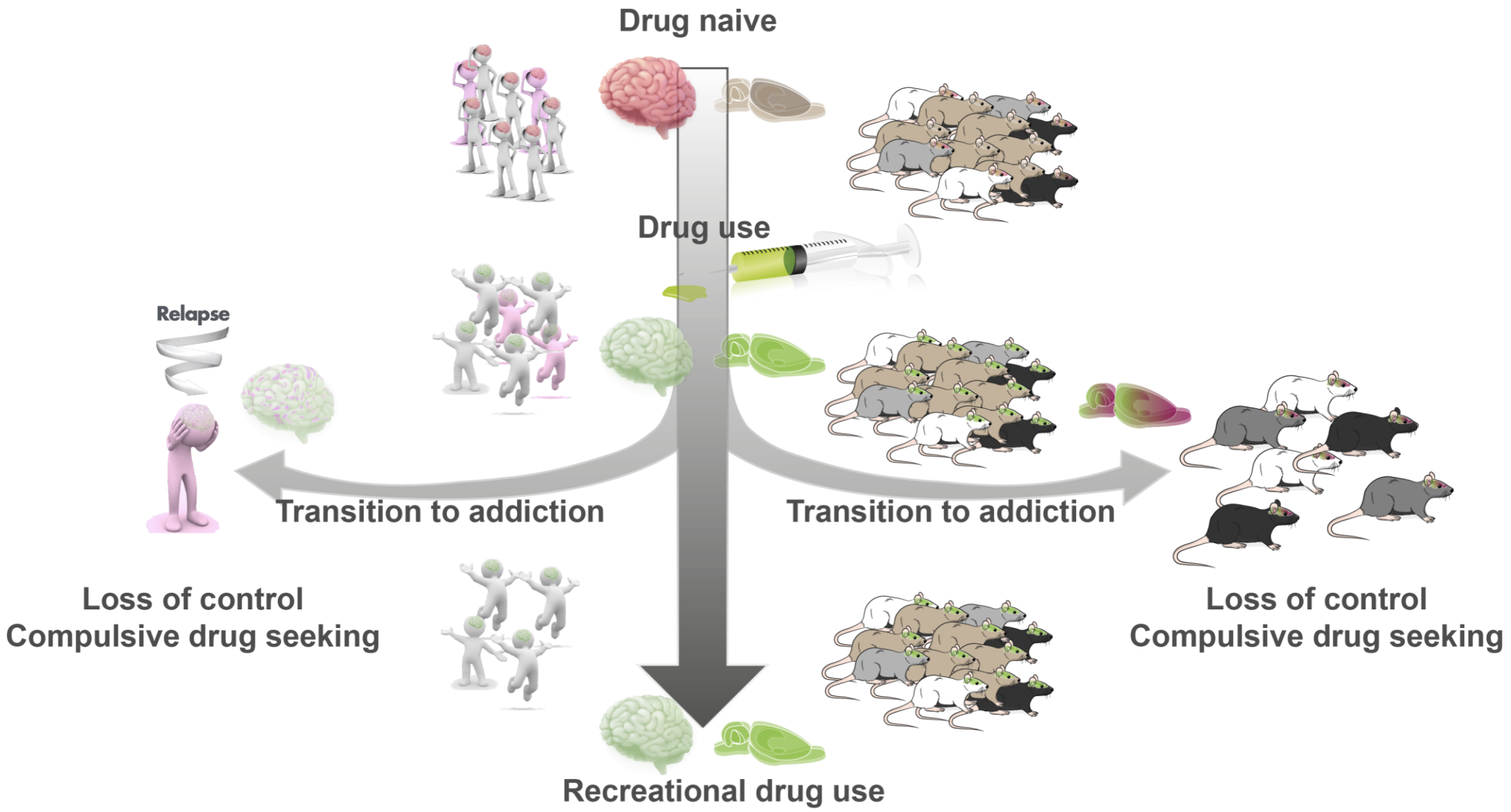
Figure 5: Performance evaluation metrics of the Machine Learning classifier of the Addiction-like behavior for alcohol in rats

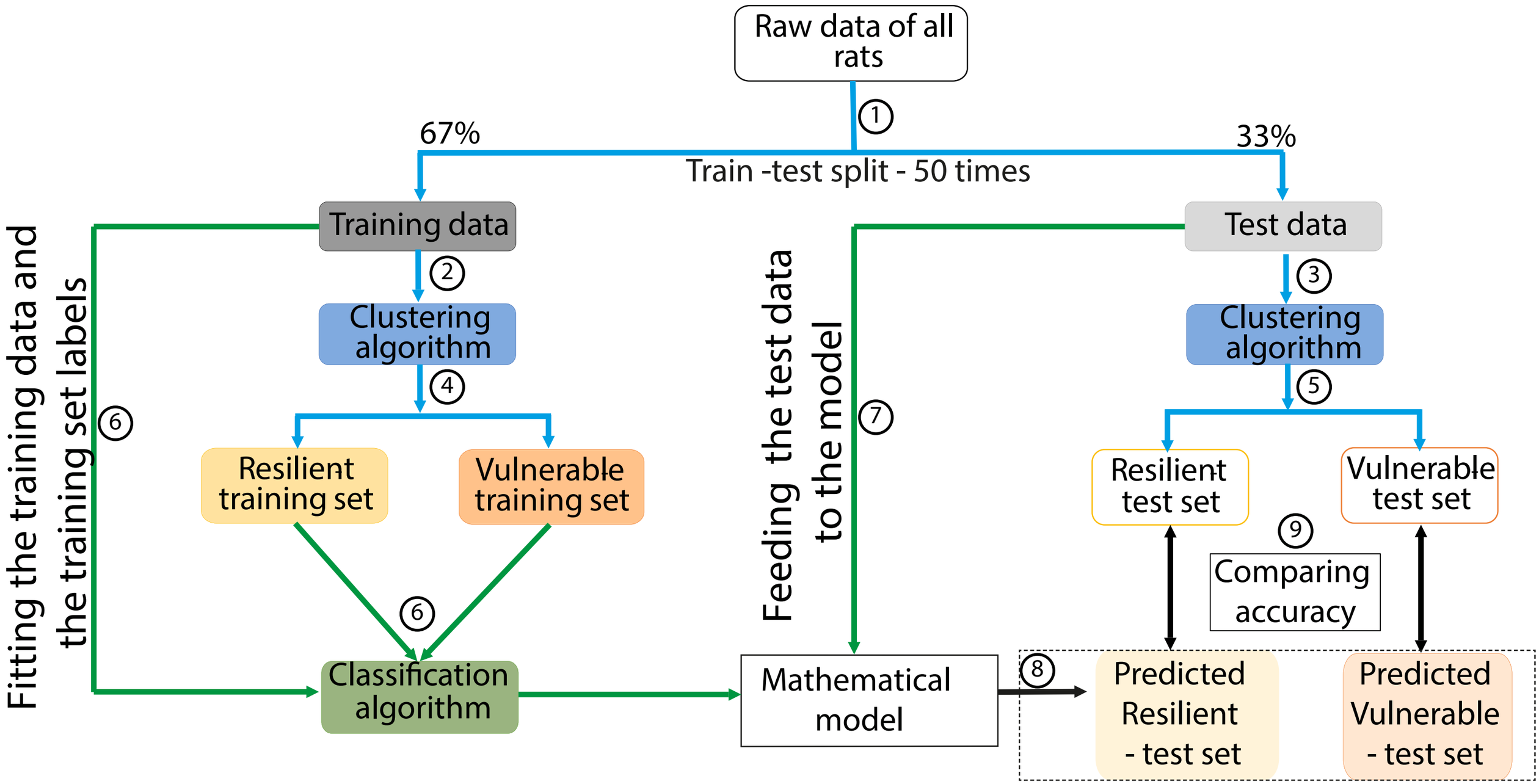
Figure 5A-5D depict the Accuracy, Precision, Recall and ROC AUC score respectively of the GMM clustering based classifier followed by four Supervised Machine Learning algorithms.
Figure 5E-5H depict the Accuracy, Precision, Recall and ROC AUC score respectively of the K-mean clustering-based classifier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

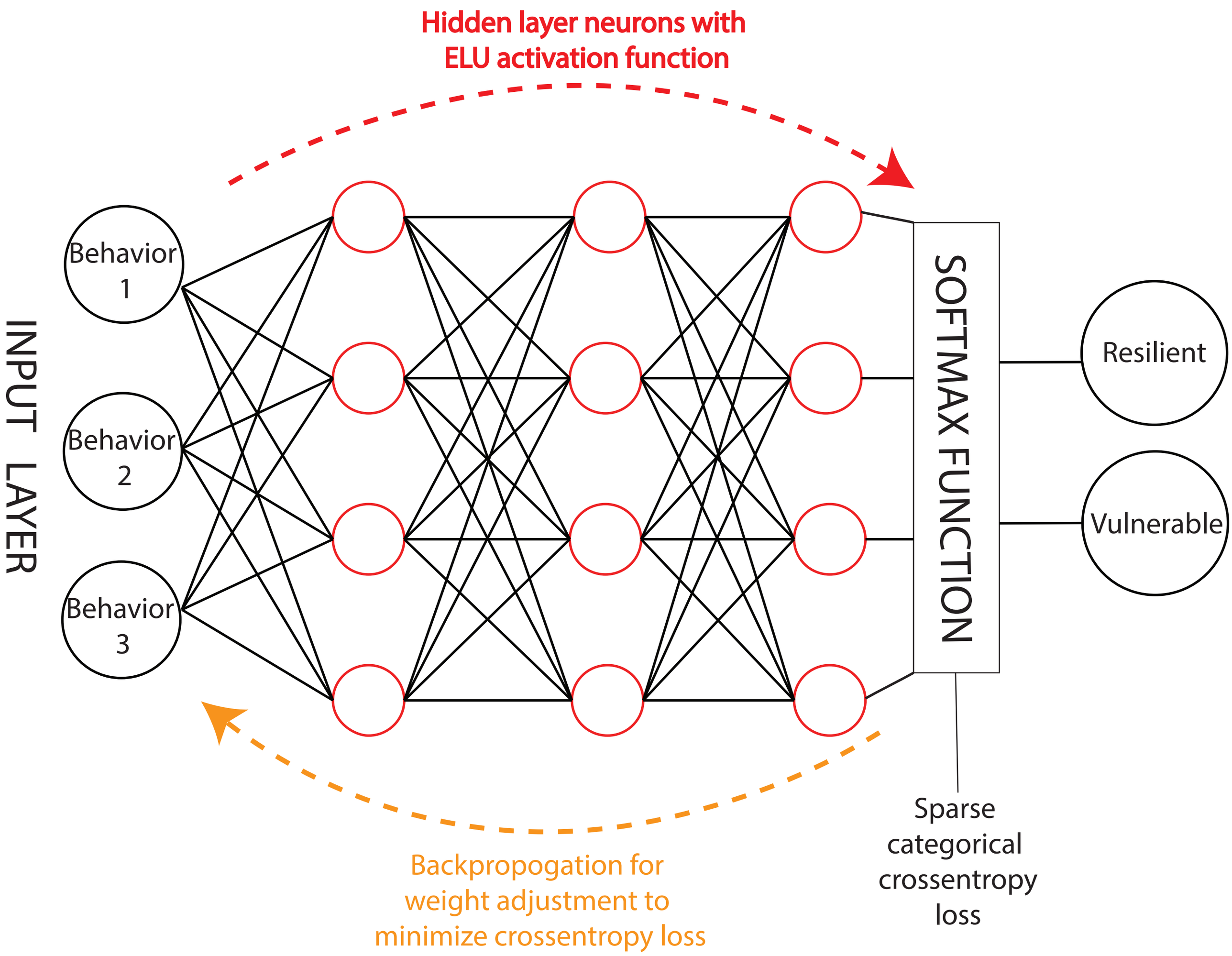
Figure 6: Flowchart of the classification of any future rat as resilient or vulnerable to SUD.

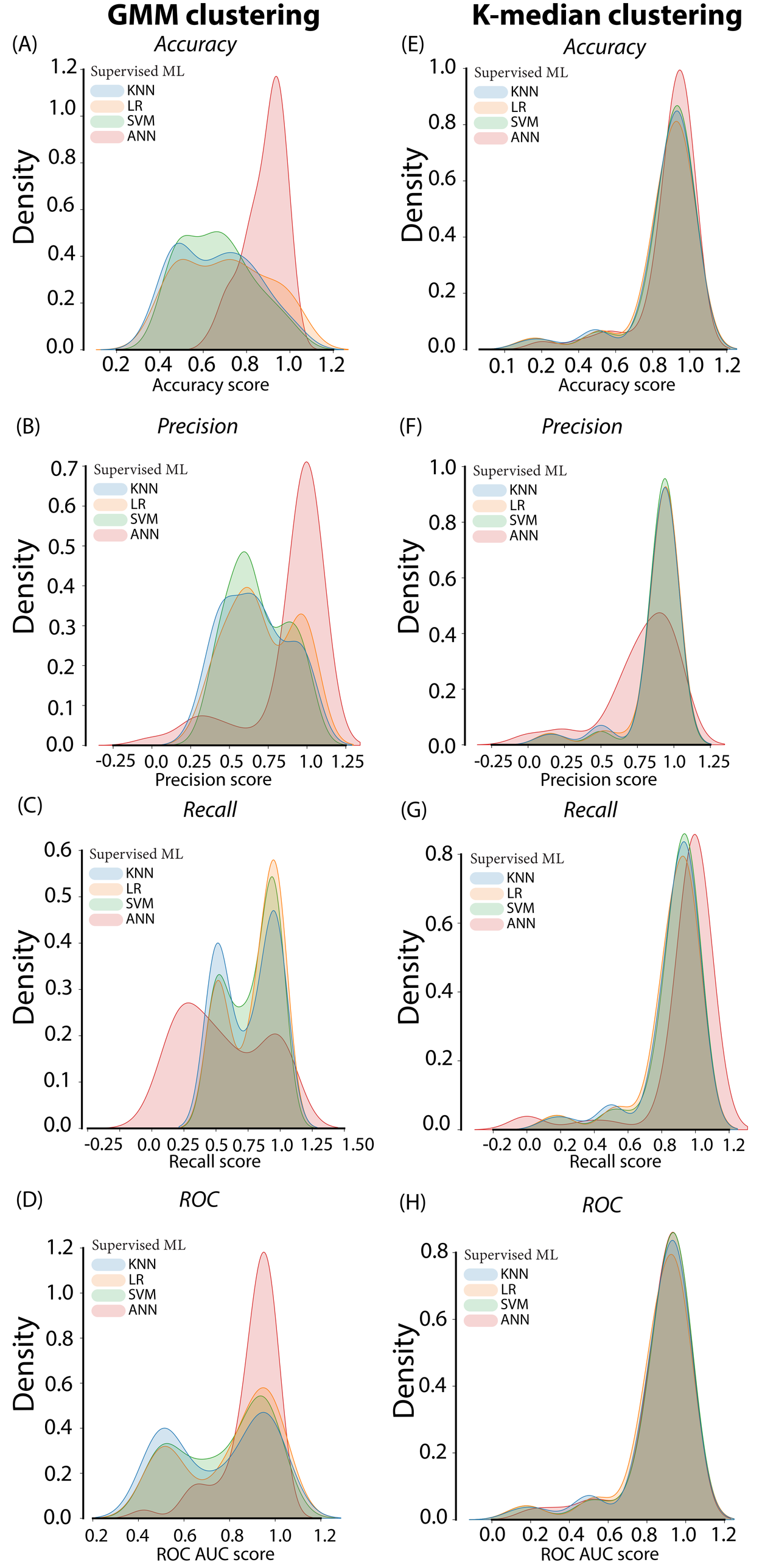
The steps are illustrated as numbers in the circles. Having established that the classifier based on K-median/K-mean clustering followed by ANN gives the best predictive accuracy, the addiction vulnerability status of a single rat irrespective of the cohort it is trained with. The blue arrows indicate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

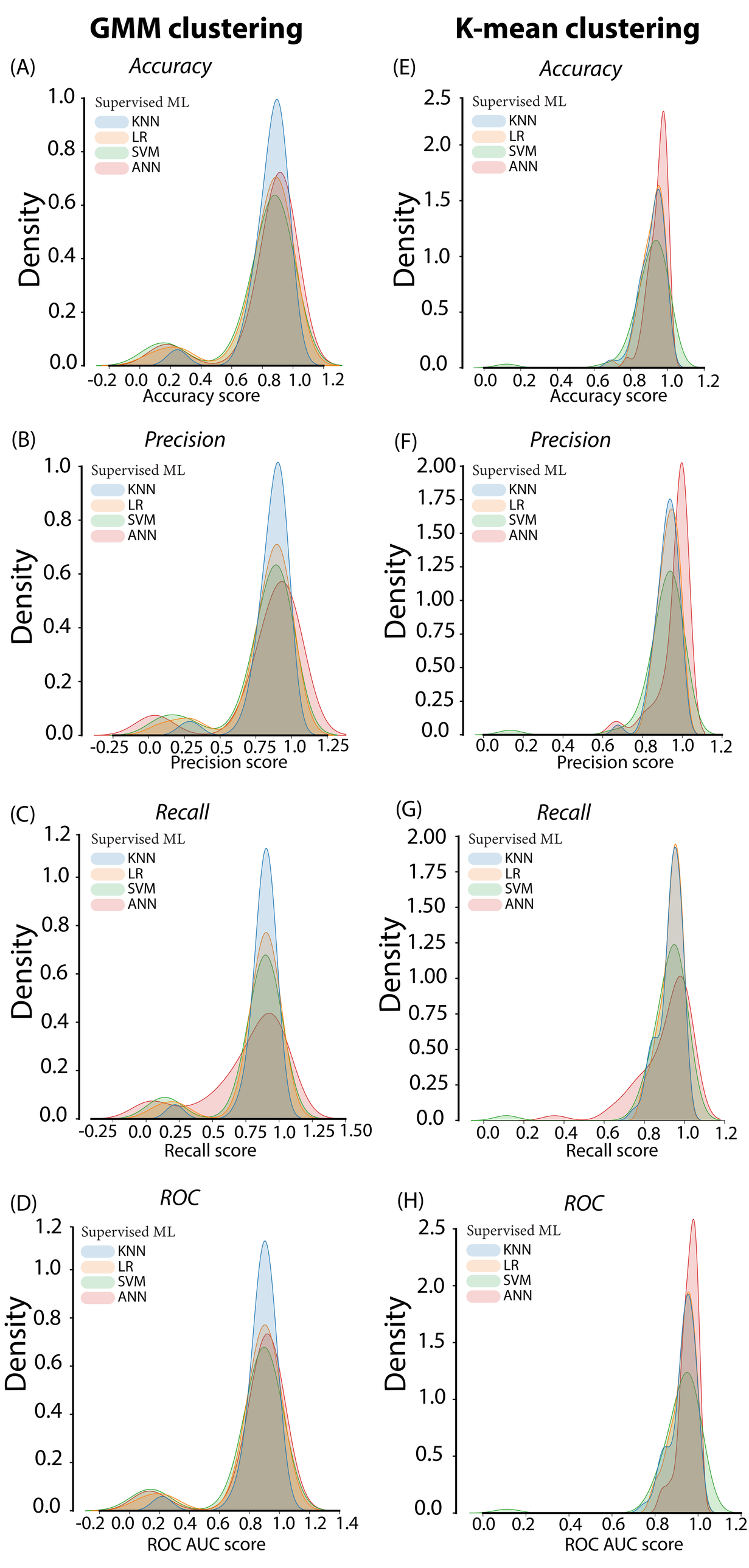
ANN: Artificial Neural Network


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
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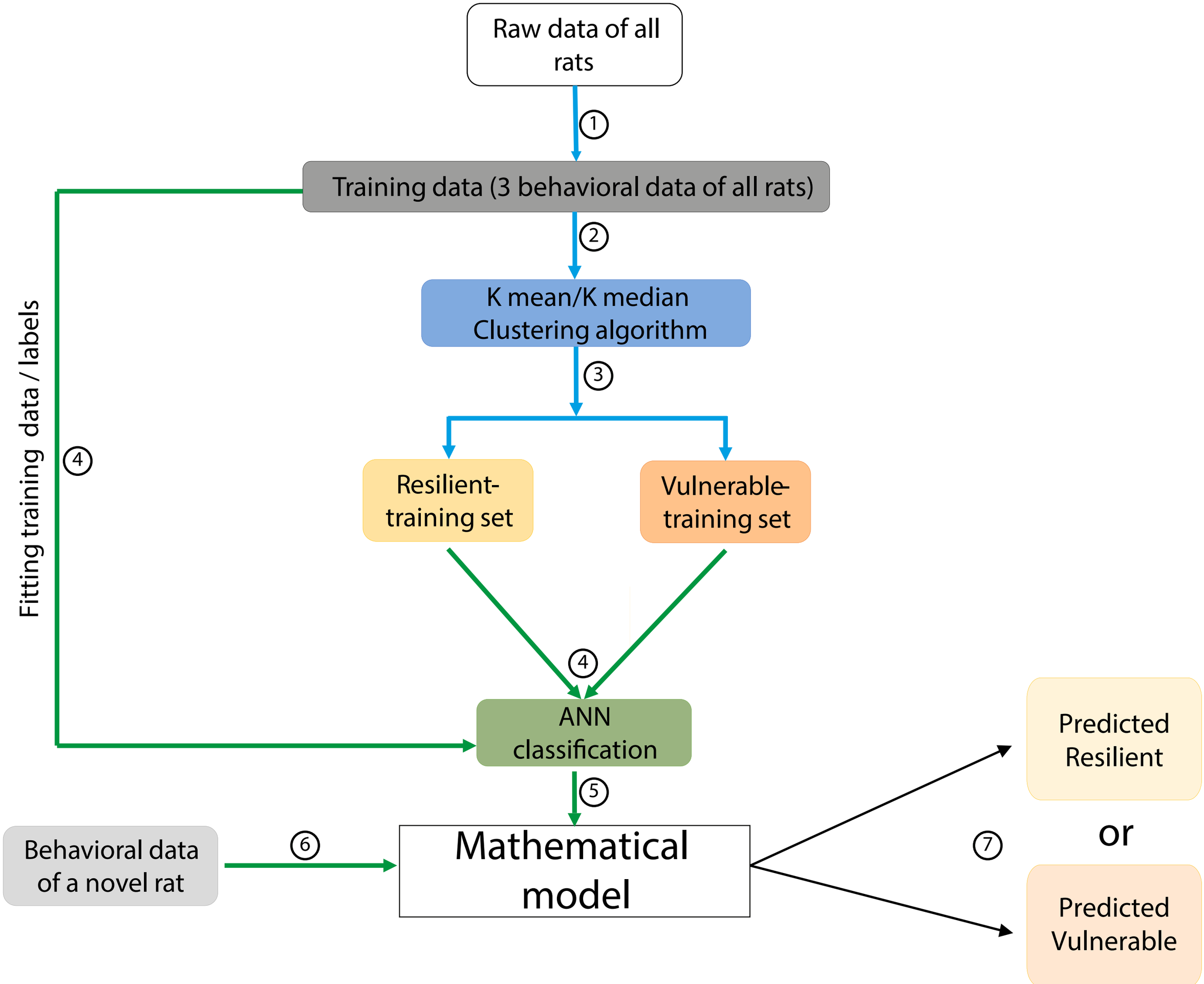
ANN
Density
ROC AUC score
(H)
ROC
Supervised ML
KNN
LR
SVM
ANN
Density
ROC AUC score


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