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Classifying and Characterizing Nicotine Use Disorder with High Accuracy Using Machine Learning and Resting-State fMRI

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Abstract

Cigarette smoking continues to be a leading cause of preventable morbidity and mortality. Although the majority of smokers report making a quit attempt in the past year, smoking cessation rates remain modest. Thus, developing accurate, data-driven methods that can classify and characterize the neural features of nicotine use disorder (NUD) would be a powerful clinical tool that could aid in optimizing treatment development and guide treatment modifications. This investigation applied support-vector machine-based classification to resting-state functional connectivity (rsFC) data from individuals diagnosed with NUD ($n=108$; 63 males) and matched nonsmoking controls ($n=108$; 63 males) and multidimensional scaling (MDS) to visualize the heterogeneity of NUD in individual smokers based on rsFC measures. Machine-based learning models identified five resting state networks (RSNs) that played a role in distinguishing smokers from controls: the posterior and anterior default mode networks, the sensorimotor network, the salience network, and the right executive control network. The classification method constructed classifiers with an average correct classification rate of 88.1% and an average area under the curve of 0.93. Compared to controls, individuals with NUD had weaker functional connectivity measures within these networks ($p<0.05$, false discovery rate corrected). Further, MDS visualization demonstrated that controls were similar to each other; whereas, individuals with NUD had less similarity to controls and to other individuals with NUD. Our findings build upon previous literature demonstrating that machine-learning based approaches to classifying rsFC data offer a valuable technique to understanding network-level differences in nicotine-related

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AUTHORS CONTRIBUTION

RRW, HR, TRF, and YF were responsible for the study concept and design. RRW, TRF, NH, and HR acquired the data. YF and JW conducted the data analyses. RRW, HR, NH, JW, TRF, and YF interpreted the findings. RRW and YF drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

neurobiology and extend previous findings by improving classification accuracy and demonstrating the heterogeneity in RSNs of individuals with NUD.

Keywords

biomarkers; fMRI; machine learning; nicotine; support vector machines

INTRODUCTION

Cigarette smoking remains a major public health problem and the leading cause of preventable morbidity and mortality in the United States (Centers for Disease Control and Prevention (CDC) 2008; 2012; World Health Organization 2008). Despite the life-threatening health consequences of smoking and the substantial economic burden on society, close to 17% of the U.S. population continue to smoke and are often unsuccessful in their attempts to quit smoking (CDC 2012; Schnoll & Lerman 2006; West *et al.* 2001). Several medical and behavioral treatments are available for nicotine use disorder (NUD), yet approximately 80% of smokers who attempt to quit smoking using available treatments are unsuccessful. Efforts aimed at improving treatment response and smoking cessation have been hampered by the absence of objective biomarkers that characterize NUD beyond self-report measures (Fedota & Stein 2015; Sutherland *et al.* 2012). Thus, developing accurate, data-driven methods with the ability to classify and characterize the neural features of NUD would be a powerful clinical tool that could aid in optimizing treatment development and guide treatment modifications.

Neuroimaging studies indicate that chronic nicotine use leads to cognitive, structural, and functional brain alterations that are evident when comparing neuroimaging data between individuals with NUD and nonsmoking, healthy controls (Franklin *et al.* 2007; Janes *et al.* 2010; Wetherill *et al.* 2014a). These neural alterations have been measured across various neural features, and most importantly, throughout neural circuits and networks underlying various cognitive and affective processes (Koob & Volkow 2010, 2016). These neural networks can be evaluated through resting-state functional connectivity (rsFC) analyses, which provides a metric of brain activity based on temporal coherence of blood oxygen level-dependent (BOLD) or perfusion fMRI signal fluctuations between disparate brain areas in the absence of an explicit task (Biswal *et al.* 1995; Fox *et al.* 2005; Wetherill *et al.* 2014b; Wilcox *et al.* 2017; Zou *et al.* 2009). As such, brain regions that spontaneously fluctuate in a highly correlated manner are termed resting state networks (RSNs) and are associated with known brain systems, such as visual, auditory, and sensorimotor systems (Biswal *et al.* 1995; Fox *et al.* 2005). Recent research in substance users has focused on the RSNs involved in addiction and other psychiatric disorders, specifically the externally focused executive control, or frontoparietal, network (ECN), internally focused default mode network (DMN), and the salience network (SN), which is thought to influence information processing by identifying the most salient information both internally and externally, and “toggling” between the DMN and ECN (Fedota & Stein 2015; Menon 2011; Sutherland *et al.* 2012; Uddin *et al.* 2011).

Although studies examining the effects of nicotine and nicotine withdrawal on rsFC suggest that nicotine and nicotine withdrawal alter connectivity between the ECN, DMN, and SN (Ashare *et al.* 2014), less is known about the effects of chronic cigarette smoking on large-scale RSNs. Using a whole-brain analyses, Weiland *et al.* found that chronic smokers show reduced connectivity within the DMN and left ECN compared to non-smoking controls (Weiland *et al.* 2015). In a study examining differences in rsFC among non-substance using controls, individuals who smoke cigarettes and drink alcohol, individuals who only smoke cigarettes, and individuals who only drink alcohol, whole-brain analyses revealed that individuals who only smoke cigarettes showed stronger connectivity within the DMN and reduced connectivity within the reward system (Vergara *et al.* 2017). Although informative, these findings are based on conventional univariate statistical analytical methods and as such are limited due to the complexities of both the disorder and the neuroimaging data. For example, findings on the effects of chronic smoking on large-scale RSNs are conflicting and not easily replicated (Vergara *et al.* 2017; Weiland *et al.* 2015). Within the neuroimaging field, machine learning-based approaches have been increasingly used to address the limitations of univariate statistical analytical approaches, as machine learning-based approaches are able to identify subtle and complex patterns in a multivariate manner and have been successful in classifying various neurobiological diseases and healthy controls based on neuroimaging data with moderate to high success (60-100% classification accuracy) (Fan *et al.* 2008a; Fan *et al.* 2008b; Orru *et al.* 2012). Pariyadath and colleagues (2014) were the first to apply a machine learning-based approach to NUD. Support-vector machine (SVM)-based classification was applied to rsFC data from 21 nicotine-dependent smokers and 21 healthy controls and found that within-network FC measures were the most informative in predicting nicotine dependence (accuracy range: 61.9-78.6%; precision range: 61.9-83.3%) and that connectivity measures within, rather than between, the executive control and frontoparietal networks were critical to this prediction (Pariyadath *et al.* 2014). In general, findings from Pariyadath and colleagues (2014) are partially consistent with earlier rsFC findings (Sutherland *et al.* 2012) and pave the way for further study in larger sample sizes using advanced multivariate techniques that can achieve improved classification success and characterization of heterogeneity in NUD.

Thus, the present study builds upon previous research by 1) applying SVM-based classification to rsFC data from individuals diagnosed with NUD and demographically-matched nonsmoking, healthy controls and 2) multidimensional scaling (MDS), a set of techniques for analysis of similarities or differences and visualization of high dimensional data (Shinkareva *et al.* 2013), to visualize the heterogeneity of NUD in individual smokers based on rsFC measures. In other words, this study uses SVM-based learning and MDS visualization to identify a biomarker that gauges an individual with NUD's deviation from matched controls. We hypothesize that our SVM approach with a larger sample will achieve better performance than the previous report (Pariyadath *et al.* 2014) and our method will characterize heterogeneity of neural features among individuals with NUD, which might help identify a neural marker of NUD severity and improve treatment planning.

METHODS

Participants

Participants were selected from a larger cohort of individuals with NUD and non-smoking controls based on demographic characteristics (for matching purposes) and head motion and included 108 individuals with NUD (63 males) and 108 demographically and motion matched non-smoking controls (63 males). All participants completed an initial telephone screen followed by an in-person screening and informed consent session. Individuals with a current DSM-IV Axis I diagnoses (other than NUD in smokers), lifetime history of head injury with loss of consciousness for more than 3 minutes, contraindications for MRI, and clinically significant medical conditions were excluded. The study protocol was executed in accordance with the standards of the Declaration of Helsinki and approved by the University of Pennsylvania Institutional Review Board.

Measures

A general demographics questionnaire assessed participant's biological sex, age, race, and years of education (Table 1). The Mini-International Neuropsychiatric Interview (Sheehan *et al.* 1998) assessed current DSM-IV diagnosis of substance dependence other than nicotine and current psychiatric symptoms. The Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.* 1991) measured severity of nicotine dependence among individuals with NUD. Individuals with NUD also reported on the number of cigarettes smoked per day (CPD), number of years of smoking, and any other substance use over the past 30 days. Urine drug screens verified the absence of illicit drugs in all subjects and the absence of nicotine and its major metabolite, cotinine, in controls.

Procedures

Image acquisition—High-resolution structural and resting-state blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) data were collected at the University of Pennsylvania Center for Functional Neuroimaging on a Siemens 3 Tesla Trio whole-body scanner (Erlangen, Germany). NUDs smoked 'as usual' on the day of the scanning session, and all NUDs smoked a cigarette to satiety approximately 25 minutes prior to the scan session. Participants were placed on the scanner table, and the head was stabilized within the head coil using foam to minimize head motion. Scan sessions involved a 10-second localizer scan to ensure good head placement and slice selection covering the whole brain, followed by a high-resolution T₁-weighted three-dimensional (3D) magnetization prepared rapid acquisition gradient echo (MPRAGE) scan (field of view (FOV)=250mm, 256×256×192 matrix, slice thickness=1 mm, repetition time (TR)=1620ms, echo time (TE)=3ms). Resting-state BOLD fMRI data were acquired using a gradient echo echo-planar imaging sequence (FOV=220mm, 64×64×64 matrix, slice thickness=4mm, TR=2s, TE=24ms, 150 volumes with no inter-slice gap). Participants were instructed to lie still in the scanner and keep their eyes open. An eye-camera outside of the scanner monitored participants' eyes to ensure that they remained awake during the scan session. All participants remained awake throughout the scan session.

Data Analysis

Each participant's rsfMRI data were pre-processed using Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, UK) and AFNI (<https://afni.nimh.nih.gov/>) software packages. Specifically, the first 6 volumes were discarded to allow magnetization equilibration. De-spiking was applied to the remaining volumes using 3dDespike, followed by slice-time correction using 3dTshift. For head motion correction, the rsfMRI volumes were realigned to the mean volume obtained by two-pass averaging using 3dvolreg. Head motion of each participant's rsfMRI data was measured by root mean square of framewise displacement (RMSFD). The rsfMRI data of each subject were intensity scaled to yield a whole brain mean value of 1,000. The rsfMRI signals of the white matter and cerebrospinal fluid, as well as 6 rigid head motion parameters, were regressed out of the data using a general linear model. Temporal band-pass filtering ($0.01 < f < 0.08$ Hz) was then performed to reduce the effects of low-frequency drift and high-frequency noise. Finally, SPM8's DARTEL toolbox was used to spatially normalize individual subject images to a group template and then normalized to the Montreal Neurological Institute (MNI) space with an affine transformation, resampled to $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$ voxels, and smoothed with a Gaussian kernel with a full-width at half-maximum (FWHM) of 6 mm.

Statistical Analysis

Independent-sample t-tests or chi-square tests (for dichotomous variables) compared differences between groups (Table 1).

Resting state network computation and identification—Group information guided independent components analysis (GIG-ICA) was used to compute subject specific resting state networks, and resting state networks at a group level were used as references to achieve inter-individual comparability of the subject specific resting state networks (Du & Fan 2013). Specifically, FSL Melodic, with its default setting, was used to compute independent components (ICs) at a group level with the number of ICs automatically estimated using Akaike Information Criterion (Beckmann & Smith 2004). The number of components was 10, and these group level ICs were then used as guidance information to compute subject specific ICs and their associated time courses using the GIG-ICA. The ICs are referred to as resting state functional networks (RSNs) hereafter.

To identify RSNs altered by NUD, we adopted a Grassmann manifold learning method to build classification models based on RSNs that were selected to optimize the classification performance for distinguishing NUD subjects from controls by the pattern classification algorithm (Fan *et al.* 2011). Rather than analyzing each RSN encoded by a spatial independent component separately, the 10 RSNs from each individual were used as bases for a linear subspace. Similarity measures between subjects RSNs were computed on the Grassmann manifold by adopting a principal angle based Riemannian distance (Harris 1992). These similarity measures were used in the support vector machine (SVM) classification. In conjunction with a support vector machine (SVM) classifier, a forward component selection technique was adopted to select RSNs for constructing the most discriminative set of RSNs. To select the most discriminative components, the forward component selection algorithm first built a classifier upon each individual RSN, the

classifier's performance was then estimated with a ten-fold cross-validation so that each RSN could be evaluated for its classification performance, and finally the component with the best classification performance was selected to be included in the classification. By combining the first selected component and one of the other components, a classifier could be built upon 2 components. All classifiers built upon 2 components were then evaluated using the same cross-validation, and the components with the best classification performance were selected to be included in the classification. This procedure was repeated to include more components in the classification one by one until one single classifier was built upon all available components and a function of classification performance of different numbers of components was obtained. Finally, across all the best classifiers with different numbers of components, the combination of components with the overall best classification performance was identified to be included in the final classification. The component selection and the classifier construction were carried out based on only training data.

Specifically, we used a 10-fold cross-validation strategy to build classifiers and evaluate their performance. The cross-validation procedure carried out a total of 10 training and testing runs. In each run, one tenth of the subjects were selected as the testing sample, and a classifier was built upon data of all remaining subjects and tested based on the left-out testing subject. The training and testing run was repeated until all subjects had been selected as testing samples. Finally, the overall classification performance was evaluated based on the 10 training and testing runs.

In each training and testing run, a classifier with the best discriminative performance given the training dataset was identified. That is, for RSNs of the training subjects, we used a nested 10-fold cross-validation procedure to select the best set of RSNs and build a SVM classifier by tuning its parameters to achieve the best classification rate. Within each run of the cross-validation, another 10-fold cross-validation was performed to select RSNs and optimize the classification parameters based on the training data (Fan *et al.* 2011). With this nested 10-fold cross-validation strategy, we built classifiers and estimated the statistical significance of our classification results using 10e5 permutation tests by building classifiers on data with randomly assigned class labels (Ojala & Garriga 2010). In addition to classification accuracy, receiver operating characteristic curves (ROCs) and the area under an ROC curve (AUROC) were also computed based on the classification scores of testing subjects (Zweig & Campbell 1993). An ROC curve provides visualization of sensitivity and specificity of a classifier at different classification thresholds; whereas, an AUROC provides a summary number of an ROC curve. A larger AUROC indicates a better classification performance. Due to inter-subject variability, the best set of RSNs for differentiating patients from HC subjects varied across training and testing runs. Therefore, we computed the frequency of RSNs selected into the best set of discriminative RSNs in all runs. The most frequently selected RSNs are the most different RSNs between NUDs and non-smoking controls. A flowchart of the nested 10-fold cross-validation is shown in Figure 1.

The nested 10-fold cross-validation classification experiment was repeated 10 times with random splits of training and testing subjects for obtaining a robust estimation of the classification performance.

Visualization of the heterogeneity of NUD in individual smokers

A Grassmann manifold distance metric (Harris 1992) measured similarity between participants based on their RSNs that are most different between NUDs and non-smoking controls. Specifically, distance to each control was calculated and then averaged for a smoker or a control subject. The distance between the same subjects was zero, indicating that our manifold distance metric satisfies “identity of indiscernibles”. Multidimensional scaling (MDS) was adopted to visualize the level of similarity of individual subjects in 2D space (mdscale, MATLAB 2014a). Based on the similarity measure, s , between two participants computed using the Grassmann manifold distance metric, functional distance between them was simple calculated as $\frac{1}{s}$. The average functional distance between controls and each individual participant measured the difference between individuals with NUD and controls.

Voxelwise FC measures of individual RSNs

Each voxelwise FC measure of one RSN was computed as Pearson correlation coefficients between the time course of the voxel under consideration and the time course of the RSN and transferred to z-scores for every participant. Then, the FC measures were compared between individuals with NUD and non-smoking controls. The statistical threshold was two sample t-tests, $p=0.05$, FDR (false discovery rate) corrected.

RESULTS

Individuals with NUD and controls were matched on age, sex, and did not differ significantly in head motion during the rsFC scan (Table 1). All subjects had RMSFM smaller than 0.4mm (NUDs: 0.14(mean) $\pm$ 0.06(std), non-smoking controls: 0.14(mean) $\pm$ 0.07(std), $p=0.70$).

Using our analytic approach, ten group level RSNs were automatically extracted and corresponding individual-specific RSNs were obtained using GIG-ICA. From these RSNs, the classification algorithm selected the posterior and anterior default mode networks (pDMN and aDMN), the sensorimotor network (SMN), the salience network (SN), and the right executive control network (rECN) as the components most frequently differentiating individuals with NUD from controls (Figure 2A, 1D). The classification method constructed classifiers with an average correct classification rate of 88.1% and an average area under the ROC curve of 0.93 (Figure 2B), indicating that our method achieved promising classification performance for distinguishing individuals with NUD from controls. The permutation test results indicated that our classification result was statistically significant ($p<10^{-6}$) (Figure 2C). The occurrences of all the RSNs selected by the classification algorithm are shown in Figure 2D. The RSNs with relatively lower frequency are shown in Supplemental Figure 1 to provide hypothesis-generating information to the field.

Voxelwise two-sample t-tests revealed that individuals with NUD had weaker functional connectivity measures within the most frequently selected RSNs than healthy controls (Figure 3).

Based on the most discriminative RSNs identified, Grassmann manifold similarity measures between participants were computed. As shown in Figure 4A, controls were similar to each other; whereas, individuals with NUD had less similarity to controls and to other individuals with NUD. The MDS visualization further demonstrated the heterogeneity of NUD based on the heterogeneity in RSNs of individuals with NUD, as they scattered further from the center of the whole sample (Figure 4B). Two-sample statistical tests (Wilcoxon Rank Sum Tests) demonstrated that NUDs had significantly larger average functional distance compared to controls (Figure 4C). We conducted post hoc correlation analyses to explore whether the heterogeneity in RSNs among individuals with NUD was associated with pre-existing smoking-related differences (i.e., years of smoking and cigarettes per day); however, findings were not significant.

DISCUSSION

This study applied SVM-based classification to resting-state functional connectivity data from individuals diagnosed with NUD and demographically-matched nonsmoking, healthy controls. The aim was to extend previous research by identifying FC measures that are predictive of NUD and apply multidimensional scaling (MDS) to visualize the heterogeneity of NUD in individual smokers based on rsFC measures. The accuracy of the SVM in classifying individuals with NUD and Controls was 88%, which is superior to a previous report (Pariyadath *et al.* 2014). Further, we were able to use this data to provide the first demonstration of the heterogeneity of NUD in individual smokers.

The rsFC of the sensorimotor, salience, default mode, and executive control RSNs predicted NUD. The predictive features of these RSNs are not surprising given that each network has been previously associated with addictive behaviors and NUD (Ashare *et al.* 2014; Lerman *et al.* 2014; Sutherland *et al.* 2012; Weiland *et al.* 2015; Yalachkov *et al.* 2012a; Yalachkov *et al.* 2012b). Although neuroimaging research on addictions typically focus on neural processes and networks associated with affective, motivational, learning and executive function, a growing body of literature suggests that the sensorimotor network contributes to the development of addictive behaviors and relapse (Yalachkov *et al.* 2010). Specifically, it is well established that nicotine/smoking-related cues acquire motivational value after repeated pairing of the smoking cue with the smoking-induced increase of dopamine (reward) in the mesocorticolimbic circuitry (Koob & Volkow 2010, 2016). This transition within reward-related circuitry is also reflected in the sensorimotor network, as frequent engagement in cigarette smoking behaviors results in deeply embedded action schemata containing motor knowledge toward obtaining and smoking cigarettes that are easily, and often automatically, triggered and easily accessible (Yalachkov *et al.* 2010). As such, the predictive value of the rsFC of the sensorimotor network could reflect the involvement of the sensory and motor processes that are triggered and are commonly engaged when a cigarette-dependent smoker prepares, and subsequently smokes a cigarette. Although speculative, additional research examining abnormalities in the sensorimotor network and its role in addiction is warranted.

As mentioned above, aberrant interactions and connectivity of the DMN, ECN, and SN are prominent features of nicotine addiction (Ding *et al.* 2017; Lerman *et al.* 2014; Sutherland *et al.* 2012, as well as other major psychiatric disorders (Menon 2011). The DMN is anchored

in the posterior cingulate cortex and medial prefrontal cortex with nodes in the medial temporal lobe and angular gyrus that collectively, are thought to be involved in self-referential mental processes. The frontoparietal ECN is anchored in the dorsolateral prefrontal cortex and the lateral posterior parietal cortex. ECN nodes show strong coactivation during many cognitive tasks, and the ECN has been linked to externally-focused tasks, including maintaining and manipulating information in working memory, problem solving and decision making in goal-directed behaviors. The SN is comprised of the insula and anterior cingulate cortex and plays a central role in cognitive control by integrating sensory information from the environment to guide attention, attend to motivationally salient stimuli, and guide neural network engagement to modulate behavior (Peters *et al.* 2016). As such, altered interactions between and within these networks can lead to cognitive control impairments and the inability to regulate behaviors, such as nicotine use.

The pattern classification method adopted in the present study identified RSNs that could distinguish individuals with NUD from controls in the Grassmann manifold learning framework (Fan *et al.* 2011). Not surprisingly, these RSNs' voxelwise FC measures were also statistically different between individuals with NUD and controls. We were able to visualize the heterogeneity of NUD in individual smokers based on rsFC measures. Overall, controls were similar to each other, whereas, individuals with NUD had less similarity to controls and to other individuals with NUD. This heterogeneity is reflected in their scatter from the center of the mean of the NUD group. The heterogeneity observed in individuals with NUD could be related to a variety of factors including an individual's genetic make-up, their environment or the known interactions between genes and environment, which help shape an individual and their smoking behavior (Li *et al.* 2017; Nilsson *et al.* 2009). For example, anxiety and stress are reduced by cigarettes/nicotine in subgroups of smokers while others use cigarettes/nicotine for the stimulating effects (e.g., weight control, concentration). Thus, our findings are the first to demonstrate the heterogeneity and complexity of NUD using brain-based, rsFC measures.

Strengths of this study include its large, well-characterized neuroimaging sample and utilization of a robust machine learning technique and multidimensional scaling to identify neural factors predictive of NUD and to characterize the heterogeneity of NUD. Limitations include the inability to account for other individual characteristics that may contribute to our findings, such as the heterogeneity of NUD imparted by genetic variance. Similarly, we were unable to determine whether these RSN differences existed prior to initiating smoking or if these differences are a consequence of smoking. In this study, we used de-spiking as a censoring technique to preprocess the rsfMRI data. The data preprocessing results and subsequently the classification results may be different if a different censor technique was used to preprocess the rsfMRI data, which merits further investigation. Although we used a rigorous cross-validation strategy (i.e., nested cross-validation for parameter optimization and component selection), we did not validate our method based on an external, fully independent dataset. Therefore, the classification model might have inferior generalization performance if it is applied to data collected using different protocols. Furthermore, the individual participants' average functional distance to controls was not independent of the groups. The group difference on the average functional distance measures might be further investigated by carrying on the Wilcoxon Rank Sum tests on the leave out folders. Future

research should seek to replicate these findings while incorporating additional factors into machine learning models.

Results from this study replicate and extend previous findings to a larger sample with better predictive accuracy and provide the first neuroimaging evidence demonstrating heterogeneity of neural features in NUD. These findings define biological deficits underlying NUD and suggest that a treatment that can strengthen connectivity between the ECN, DMN, and SN might be an effective smoking cessation medication. Thus, our data provide additional evidence for combining rsFC data with machine-learning techniques and multidimensional scaling to improve our understanding of network-level differences predictive of NUD and characterizing individual differences among individuals with NUD, which can aid in optimizing treatment development and guide treatment modifications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Flowchart of the nested 10-fold cross-validation. The dataset is randomly partitioned into 10 subsets and each of them has the same proportions of individuals with nicotine use disorder and controls. Of the 10 subsets, 9 subsets are used as training data to build a classification model, and the remaining subset is retained as the test data for testing the classification model and estimating the classification performance. The cross-validation process is then repeated 10 times (the folds), with each of the 10 subsets used exactly once as the test data. The 10 results from the folds are then pooled to estimate the classification performance. To build the classification model for each fold, a 10-fold cross-validation is used to select the best set of resting state networks (RSNs) and optimize support-vector machine (SVM) parameters.

Figure 2.

The left panel A) shows the five functional networks most frequently contributed to the classification for differentiating individuals with nicotine use disorder (NUD) from healthy controls. The top right graph B) shows the receiver-operating characteristic (ROC) curves of ten repetitions of 10-fold cross-validation results. The middle right graph C) shows the permutation classification rates of 10e6 permutation tests and real classification rates of 10 repetitions of the cross-validation results. The bottom right graph D) shows the frequency of different resting state functional networks selected in the cross-validation experiments. Brain regions shown in the networks display voxelwise t values of one sample t-tests of functional connectivity measures of all participants, as indicated by the colorbar ($q < 0.05$, false discovery rate (FDR) corrected). SMN = sensorimotor network; SN = salience network; aDMN = anterior default mode network; pDMN = posterior default mode network; rECN = right executive cognitive network; VAN = ventral attention network; VN = visual network; DAN = dorsal attention network; IECN = left executive control network; DMN = default mode network

Figure 3.

Voxelwise differences in functional connectivity of the most frequently selected resting state networks (RSNs) between individuals with nicotine use disorder (NUD) and controls. Brain regions shown in the networks display voxelwise t values of two sample t-tests of functional connectivity measures between individuals with NUD and controls, as indicated by the colorbar ($q < 0.05$, false discovery rate (FDR) corrected). SMN = sensorimotor network; SN = salience network; aDMN = anterior default mode network; pDMN = posterior default mode network; rECN = right executive cognitive network

Figure 4.

The top graph A) displays the Grassmann manifold similarity measures between participants, calculated based on the top 5 most frequently selected resting state networks, depicting pairwise similarity between participants of this study. The middle graph B) represents the multidimensional scaling visualization of the functional distance between participants of this study, revealing heterogeneity of individuals with nicotine use disorder (NUD) with respect to their functional similarity (the x and y axes are two dimensions identified by mdscale, inversely proportional to inter-subject similarity measures). The

bottom graph C) shows the individual participants' average functional distance to controls, highlighting group difference between individuals with NUD and controls with respect to their functional similarity.

Table 1

Participant demographic and smoking characteristics

	Individuals with NUD (<i>n</i> =108)	Controls (<i>n</i> =108)	<i>p</i> -value
Sex	63 males	63 males	1.00 ^{<i>a</i>}
Age	35.7±11.6	34.5±8.7	0.41 ^{<i>b</i>}
Years of Education	14.4±2.3	14.8±2.1	0.19 ^{<i>b</i>}
Ethnicity	43 Caucasians	33 Caucasians	0.32 ^{<i>a</i>}
	51 African Americans	64 African Americans	
	8 Asian Pacific Islanders	5 Asian Pacific Islanders	
	6 Other	6 Other	
RMSFD	0.14±0.06	0.14±0.07	0.70 ^{<i>b</i>}
FTND	4.7±1.7	–	–
Cigarettes/Day	13.8±15.4	–	–
Pack Years	11.5±9.3	–	–

NUD, nicotine use disorder; RMSFD, root mean square of framewise displacement to measure head motion; FTND, Fagerström Test for Nicotine Dependence,

^{*a*} chi-square test

^{*b*} two-sample *t* test