MACHINE-LEARNING-BASED CLASSIFICATION OF ACUTE PARTIAL SLEEP DEPRIVATION WITH RESTING-STATE FMRI

by

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DISSERTATION ABSTRACT

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Insufficient sleep is highly prevalent. Limited knowledge has been accrued on the functional correlates of acute partial sleep deprivation in the awake brain. As resting-state functional magnetic resonance imaging (rs-fMRI) becomes an essential measure to investigate spontaneous neural activity and intrinsic functional connectivity, applying machine learning to rs-fMRI to classify the state of acute partial sleep deprivation remains an uncharted area. In the present study, based on sleep deprivation literature, a set of predetermined rs-fMRI region and network functional connectivity features were used to classify the sleep states (sleep deprived/well-rested) of the senior (N = 34, age 65-75) and young adult (N = 41, age 20-30) participants in an archival dataset. The best performing support vector machine model classified the sleep states of the senior adult participants with a 68% accuracy rate. During external validation, this model trained on senior adults demonstrated low transferability to the young adult dataset. Low classification accuracy were reported in models trained on young adult dataset. The theoretical implications of the findings and recommendations for future research were discussed to contribute to a multi-modal understanding of the mechanism of sleep insufficiency as a causal factor of neural vulnerability and inform neurobehavioral interventions.

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I: Introduction

Sleep insufficiency and physio-behavioral influences

Humans spend approximately one third of the lifetime sleeping. Despite a universal, evolutionarily and clinically important behavior, the neurobiological mechanisms of sleep deprivation remain poorly understood [1,2]. Between 25% [3] and 44% [4] of the adults reported sleeping less than the recommended 7-9 hour per night. Adults' sleep insufficiency may partially arise from insomnia symptoms: difficulty initiating sleep (23%) is most prevalent in young adults (age 18-25 years), whereas difficulty maintaining sleep (23%) and early morning awakening (24%) are most frequent among senior adults (age > 65 years) [3].

Maintaining adequate sleep opportunities is challenging to young and senior adults for varied reasons. Biologically, normative developmental delays in the body's internal clock render sleep timing at its latest at around age 20 [5]; Behaviorally, young adults' academic and work responsibilities prevent them from compensating for the late sleep timing by sleeping in the next day, causing "social jetlag" [6,7]. Among senior adults, in addition to sleep pattern changes with normative aging, 50~60% of senior adults reported sleep disturbance due to multiple factors as sleep disorders, medical and psychiatric conditions, related medication use, and socioenvironmental changes [8].

Sleeping less than six [9,10] or seven hour [11] is robustly linked with worse cardiometabolic health [12,13] and all-cause mortality [14]. Risk of motor vehicle accidents doubles from sleepiness at the wheel [15]. Much more than a secondary condition, poor sleep health is a critical indicator and risk factor of physical and mental health issues, thus sleep and determinants of sleep health are increasingly recognized as valuable modifiable factors with etiological and clinical implications [16]. Sleep deprivation is a condition that destabilizes cognitive functioning and this mostly

reversible sleep condition can be experimentally perturbed to enrich the knowledge base of the neural mechanisms underlying sleep and cognitive instability, providing unique predictive information about individual functioning for typical developing and clinical populations across ages [17].

In experimental settings, sleep deprivation impairs all major domains of human functioning [18]. Within the sensorimotor system, sleep deprivation heightens subjective pain intensity, lowers peripheral/central pain thresholds [19], and disrupts motor/balance control [20] and physical performance [21]. In the cognitive system, heightened homeostatic sleep drive from a period of short-term total sleep deprivation deteriorates cross-span cognitive components: accuracy, processing speed, short-term memory (declarative and procedural) [22], complex attention, working memory and simple attention [23]. Simple attention or vigilance, with least compensating resources available (e.g., neurobiological, behavioral), is the fundamental process deteriorated by sleep deprivation [24] in a dose-dependent manner [25]. Linking the sensorimotor and cognitive systems, acute sleep deprivation impairs task-goal switching [26] and visual/perceptual inhibitory control [27]. Extending to the arousal/regulatory systems, sleep deprivation disrupts diurnal modulation from the circadian timing system on inhibitory control [27]. The negative and positive valence systems are also impacted by sleep deprivation [28,29] in forms of poor inhibitory control and lowered speed and accuracy of emotion processing [30], leading to more intrusion of unwanted thoughts [31], effort discounting, risk taking, and sensation seeking [32]. Lastly, sleep deprivation diminishes socioemotional functioning via altered emotional reactivity, evaluation, and expression [33–35] within the social processes systems.

Given the high prevalence and significant physical and psychological impact of sleep deprivation, building an accurate account of sleep deprivation induced neural activity aberration

is important to 1) explain behavioral impairment by characterizing regional and network activities that are vulnerable and resilient to sleep deprivation (thus extended wakefulness), 2) understand the etiological and maintaining roles of sleep deprivation in major neurological and psychiatric conditions, and 3) promote public health advocacy for industrialization-related sleep-loss issues [32].

Task-based neural correlates of sleep insufficiency

Although sleep deprivation affects whole-body functioning, no other organ is as severely affected as the brain [36] and such consequences can only be compensated with sleep itself [2]. Sleep deprivation burdens the integrity of neural functional architecture [37]. An abundance of research has reported that the neurobehavioral effects of sleep deprivation mirror the alterations of neural activations found in task-related functional magnetic resonance imaging (fMRI) studies across the Research Domain Criteria [18].

In the sensorimotor system, one full night of acute sleep deprivation amplifies thermal pain reactivity within the primary somatosensory cortex, predicting lowered pain thresholds, yet blunts pain reactivity in the striatum and insula cortex (involved in higher-order valuation and decision-making) [38]. One night of acute sleep deprivation also impairs learning and encoding performance with reduced hippocampal functional connectivity (FC) with perceptual regions of the occipital cortex and the medial temporal lobe and increased hippocampal connectivity with subcortical regions as the brainstem and the thalamus [39].

Within the cognitive domain, sleep deprivation causes a global curtailment of processing resources, decreasing activation in extrastriate visual cortex for visual perception and fronto-parietal regions for the mediation of the top-down control of attention [40]. Meta-analyses of neuroimaging studies with varied attention tasks concluded that acute total sleep deprivation

heightens thalamic activation, possibly as a compensatory response to maintain attentional performance, and lowers activation in executive function regions as the anterior cingulate cortex (ACC) [41], the salience network [SAN; insula and medial prefrontal cortex (mPFC)] and the fronto-parietal attention network [PFC and intraparietal sulcus (IPS) [42]]. Such lowered salience-detection network activity post sleep deprivation may hint at sleep deprivation disrupting the right frontoinsular cortex's control on switching between the central executive and the default mode network (DMN) activity [43], leading to unstable gating between on-task functional and off-task DMN activity [32]. Substantial post acute sleep deprivation reduction in thalamic activity positively correlates with lapses in attention [44]; Such inconsistency is explained that acute sleep deprivation causes instability in thalamus' gating hub capacity to ascend arousal-promoting input (from the brainstem) to the cortical attentional networks [32]. In summary, sleep deprivation reduces activation in extrastriate cortical regions, causes maladaptive frontoparietal and frontoinsular gating of on-task relative to off-task network control, and induces alterations in thalamic activity and connectivity, impairing both attention and working memory [32].

Compared with well-rested participants, fully sleep deprived participants reacted to negatively-valenced stimuli with stronger amygdala activation, along with lower amygdala connectivity with the mPFC and higher amygdala connectivity with autonomic-activating centers of brainstem, suggesting reduced top-down, prefrontal control [45]. Acute sleep deprivation elevates activity in the amygdala, anterior insula and ACC in anticipation of cued (aversive) emotional experiences, especially for individuals with high trait anxiety [46]. Sleep deprivation also causes impairment in emotional discriminatory specificity [47]: an overall bias towards increased perception of negative social threat within the viscerosensory regions of the anterior insula, ACC and the subcortical amygdala [48], and low empathetic sensitivity [49] related to the interoceptive

processing network of the insula, mPFC and amygdala [50]. One cellular and molecular mechanism underlying sleep-deprivation-associated emotional discrimination inaccuracy may be that the overnight reduction of rapid eye movement (REM) sleep leads to heightened locus coeruleus noradrenergic tone [51], which innervates the affective SAN [47]. In general, sleep deprivation appears to exaggerate negative affective experiences while impairing emotional regulation.

Sleep deprivation generally increases reward sensitivity and impairs reward-value discrimination, updating, and integration accuracy [32]. Sleep deprivation and extended wakefulness alter activation within the mPFC, orbito-frontal cortex (OFC), ACC, anterior insula, ventral striatum, and basal ganglia, which corresponds with amplified and/or inaccurate representation of reward/punishment value, leading to non-optimal (short-sighted) reward-dependent decision making and actions [52–55]. Ventral-medial prefrontal cortex in particular could be involved in valuation of positive emotions, aiding stress recovery [56] and performing goal-directed inhibition and control [57]. Sleep disruption's impact on reward-related functions is sensitive to interacting factors as blunted trait-level reward responsivity [58]. The counter-intuitive rapid, nonpharmacologic antidepressant effect from acute sleep deprivation [59] is mostly caused by a series of downstream effects: an accumulation of adenosine [60], a reduction in dopamine D2 and D3 receptors availability [61], and an increase in dopamine binding to the remaining D1 receptors reflected as enhanced fMRI striatal activity [62], which is linked with approach and reward related behavior [32]. Overall, sleep deprivation increases impulsivity and reduces effectiveness in approach and reward related behavior.

Resting-state (rs) fMRI sleep deprivation research

In addition to the piecemeal use of task-based functional imaging testing a single domain at a time, rs-fMRI studies provide cross-paradigm insight on the pervasive impact of sleep

deprivation on neural connectivity. FC Magnetic Resonance Imaging aims at quantifying functional integration across neural regions with blood-oxygen-level-dependent (BOLD) signal temporal correlations. Rs-fMRI records a rich repertoire of intrinsic mental states [63] and serves as a promising clinical tool to study the functional architecture of the brain [64]. Across various modalities of neuroimaging data, rs-fMRI is increasingly used to examine neural connectivity and biomarkers of psychiatric disorders [65]. In addition to sleep diary and participants' self-report on their subjective level of sleepiness, rs-fMRI may enrich a multi-modal depiction of the impact of sleep deprivation with objective network-level biomarkers and functional changes.

Rs-fMRI studies revealed that total sleep deprivation impairs rs-visual-parietal FC and enhances ACC and the insula FC, suggesting decreased information reception and compensation in the executive networks [66]. Sleep deprivation induced dynamic FC alterations include 1) regional-level temporal variability increases within large-scale brain regions, 2) decreases among thalamus subregions, 3) intra-network temporal variability increases within the DMN, and 4) inter-network temporal variability increases within subnetwork pairs, including the variability between visual network and DMN, which suggests low processing speed [67]. An activation likelihood estimation meta-analysis concluded that acute sleep deprivation reduces task-based fMRI activation in the right parietal cortex (specifically, the right IPS) and superior parietal lobule (SPL) [68] and decreases rs-fMRI co-activation in the IPS, SPL, insula, thalamus, cerebellum, inferior frontal gyrus (IFG), precentral gyrus, and caudal and dorsal lateral occipital cortex [68]. As IPS and SPL are the critical nodes of information computation for choice of an action [69], this may explain why sleep deprivation impairs decision-making and highlights parietal cortex's role in sleep-deprivation-altered connectivity within the frontoparietal network [70]. In summary, major rs-FC changes post sleep deprivation are a loss of integration within the DMN

network, between the salience and attention systems, reduced segregation between networks, and global signal increase [71].

As shown in the summary above, sleep deprivation related FC alterations highly converge between rs- and task-based fMRI studies. The links between structural and FC are robust as anatomical white matter (WM) connectivity properties indicate and can be inferred from the strength of rs- and task-based functional correlations [72]. Task-based and rs-fMRI are correlated and complementary, with the former technique providing superior localization and the latter offering a flexible, accessible, and scalable approach for characterizing brain function [73]. A two-stage dictionary learning framework confirms intrinsic differences within fMRI signal composition patterns as they can differentiate task-based and rs-fMRI [74]. Multi-task co-activation matrices, especially within parietal and occipital macroscale brain regions, are functionally meaningful and predict concurrent and prospective rs-DMN connectivity [75]. Individual task-based brain activity can be predicted from rs-FC [73] and meta-analytic coactivation patterns from task-based fMRI correspond well with the rs-connectivity and network [76]. During task performance, the coactivation network features higher global efficiency, smaller mean clustering coefficient, and lower modularity compared to off-task states, suggesting the whole brain is efficiently connected to support global information flow with stronger dynamic connectivity between brain systems [76]. Hubs shift between task and rs as the thalamus mediates corticocortical communication during tasks whereas the left inferior temporal cortex, a part of the DMN, shows high centrality during rs [76]. In addition to a strong physiological bases in the study of rs-fMRI FC, advanced techniques as machine learning (ML) further enhances rs-fMRI FC research.

Machine-learning applications in rs-fMRI research

The interpretation of complex rs-fMRI data is highly interdisciplinary and sleep research utilizing rs-fMRI has only recently emerged due to the development of state-of-the-art techniques rooted in ML [63]. ML, the science of discovering patterns in a relatively model-free manner, can characterize rs-fMRI data while taking into account inter-regional correlations, as it detects subtle and spatially distributed effects, and differentiates between groups [77]. Machine learning classifier (MLC) methods or multi-voxel pattern analysis (MVPA) are increasingly being applied to neuroimaging data to detect model-free patterns of brain activity that could differentiate between conditions [78,79].

MLC of fMRI data composes three stages: 1) extracting features from the fMRI data, 2) selecting features to be included in the classifier analysis and reduce redundancy, and 3) training the classifier in the training dataset and testing the accuracy of the classifier in testing datasets with cross-validation techniques [79,80]. In fMRI analyses, the combination of small sample sizes and vast features could lead to overfitting in classification with poor generalizability [79,81]. Feature selection helps and MLC can be performed with support vector machine (SVM) [82,83], a powerful method suitable for small training dataset with ideal prediction accuracy, efficiency, simplicity, and robustness [84–86]. SVM was reviewed to be the most popular method in single subject prediction of neural disorders in neuroimaging [87]. Whereas traditional univariate voxel-based methods as the general linear model may overlook meaningful yet statistical non-significant neural signals [88,89], SVM can identify voxels or neural regions of interest containing differentiating information to classify groups by accumulating the information efficiently across spatial locations [77,78]. Such higher sensitivity could reveal subtle and spatially distributed differences (e.g., inter-regional correlations), which could be undetectable with group

comparisons [90]. Given probable widespread changes in functional networks from sleep deprivation, SVM could be an ideal candidate to investigate subtle pattern changes.

SVM is the most widely used classification algorithm in the analysis of rs-fMRI dataset and it generally manages well with high-dimensional data due to an implicit regularization [63]. This multivariate pattern recognition ML technique is well-suited for discriminating high-dimensional rs-FC fMRI data [91]. In supervised classification of psychiatric disorders, most of the prediction models are based on standard kernel-based SVMs with FC between regions of interest (ROI) pairs as the input features [63]. A recent systematic review and meta-analysis of MLC applications in rs-fMRI on Autism Spectrum Disorder concluded that the clinical application displayed acceptable to excellent sensitivity (73.8%) and specificity (74.8%), and among the 55 studies under review, SVM was the most used classifier (76%) [65]. SVM-based models with rs-fMRI features could also differentiate hunger from satiety states with a classification accuracy of 81% [92]. In this study, the amplitude based connectivity model outperformed the local and global connectivity models [92]. With SVM, an upper bound on generalization error has been found to be independent of the number of features [93]. SVM-based classification application in clinical and fMRI research is important as it further complements conventional group level analyses.

Group level analysis and classification are different methods addressing different questions [87]. Regardless of the data type, statistically significant explanatory variables cannot automatically imply strong predictivity and highly predictive variables do not necessarily appear as statistically significant [94]. Explanatory variables are typically identified based on some variation of linear regression and work for significance-based research questions [94]. For classification-based research questions, explanatory variables might not work well, whereas, cross-validated prediction models focus on identifying variables with high predicative power in

condition classification [94]. For instance, contrasted with measures of central tendency (mean accuracy, error rates), measures of intra-individual variability (standard deviation, coefficient of variation) more effectively differentiated cognitively impaired (e.g., following sleep deprivation) and clinical groups (e.g., Attention-Deficit/Hyperactivity Disorder) from healthy controls [95]. Statistics on classification with major applications to biology has a long-established literature [94] and ML has been applied to neuroimaging over two decades [87]. Analyses based on contrasts among groups are valuable in identifying relevant disease biomarkers, yet insufficient for direct clinical diagnostic/prognostic adoption [87]. Statistically significant findings at the group level do not equate the individual discrimination ability of the proposed biomarkers [87]. Classification, by providing information for each individual, is considered a much more challenging task than reporting group differences [87].

ML-based-classification in sleep deprivation fMRI research

In the last decade, ML has gradually been applied to the analysis of sleep deprivation induced perturbations in neuroimaging research. The first attempt to classify the state of sleep deprivation with fMRI FC data was published by Gujar and colleagues [96]. With a between-subject design (N = 26, age 18-30 years), one night of total sleep deprivation disrupted task-induced deactivation of DMN with less and greater deactivation in the dorsal-ACC and precuneus respectively; the degree of the altered deactivation classified the sleep deprivation state among the participants with 93% sensitivity and 92% specificity [96]. In another study (N = 52, age 17-23 years) collecting T1-weighted MRI data, linear regression with least absolute shrinkage and selection operator (LASSO) were applied to show that gray matter (GM) volumes in multiple regions could accurately predict the response inhibition impairment post acute total sleep deprivation [97]. Of note, the first study examined task-induced deactivation rather than rs-

scans, which may offer more unconstrained examination of sleep deprivation caused rs-network alterations [96]; the second study focused on individual brain structural differences.

To date, five studies on sleep deprivation have applied ML based classification with rs-fMRI data. In one study featuring a mixed design (N = 60, age 18-26 years), a regularized linear discriminant analysis classifier labeled the FC data post total sleep deprivation with an 85.4% accuracy rate and the univariate statistics displayed widespread and robust post acute total sleep deprivation FC alterations independent of diurnal variability (dorsal attention, default mode, visual, frontal, auditory, cerebellar, motor and hippocampal networks) [1]. Co-activation among these regions, precuneus (the functional core of DMN), middle occipital gyrus (visual), vermis (cerebellar and motor) and hippocampus, have been observed and interpreted as highly DMN-related activities as mental imagery and memory [98]. In addition to static FC, in one study (N = 26, age 23.1 +- 1.9 years), the dynamic/temporal properties of the FC states (the dwell time and probability of state transitions) negatively correlated with DMN-dorsal attention network (DAN) connection strength (signaling vigilance) and effectively distinguished the rs-brain networks pre and post 36 hours of acute total sleep deprivation with an accuracy rate of 88.6% [99]. Thus the occurrence frequency of FC states may result in static FC findings and the use of dynamic framework may out-perform static FC in state classification [99]. A data-driven whole-brain graph-based analyses of the functional graphs from rs-fMRI data with a within-subject design (N = 17, age 23-33 years) revealed that acute total sleep deprivation caused a breakdown of the brain's global function organization (a loss of functional segregation), including behavioral impairment correlated changes in the modularity structure of emotional, salience and default mode regions [100]. This study achieved a classification accuracy of 76.5%. In a recent study (N = 59, age 22 years), graph-theory-based measures were combined with SVM to highlight that degree

centrality within sensorimotor network, DMN and thalamus during the rested wakefulness scans accurately classified (84.75%) individual vulnerability to acute total sleep deprivation [91]. Also with a SVM classifier, which was trained on the FC data in the well-rested state, the model classified 41 of the 68 subjects' acute total sleep deprivation vulnerability and resilience states with an accuracy rate of 60.3% [101]. These five important studies achieved varied levels of accuracy rate in the application of interdisciplinary techniques to classify the state and individual susceptibility to the impact of total sleep deprivation with task-based and rs-fMRI FC data.

All these key studies on total sleep deprivation incorporated a uniform sample of young adults. In the Stockholm Sleepy Brain acute partial sleep deprivation study, Nilsonne et al. recruited both young and senior adults. Because of age-related increases in compensatory effects post sleep deprivation [102], it is meaningful to study compensatory and non-compensatory deprivation-induced connectivity alterations in this sample with young and senior adults. The analysis of the rs-FC data from Nilsonne et al.'s study indeed replicated the age effect on FC. Meanwhile, in comparison to total sleep deprivation, partial sleep deprivation's impact on FC may be more elusive. In one study, partial sleep deprivation reduced FC between posterior cingulate cortex (PCC) and ACC, and increased FC between dorsal nexus (a cortical area in the dorsal-medial PFC) and right dorsal-lateral PFC; both are consistent with the neural connectivity alteration correlated with the transient antidepressant response [103]. In contrast, Nilsonne et al.'s study did not fully replicate the expected impact of sleep deprivation on intra and inter FC within DMN, task-positive networks including using indexes as regional homogeneity (ReHo), Amplitude of Low-Frequency Fluctuations (ALFF). They concluded that partial sleep deprivation caused no statistically significant rs-FC group differences other than the increased

global signal variability, signaling wake-state instability, among young and senior adult participants [104].

The present study

In the present study, ML techniques will be applied to extend the conventional group-level rs-fMRI analyses conducted by Nilsonne and colleagues [104]. Whereas group-level techniques have been applied to identify average between-group differences, ML techniques may make better predictions on individual participants [81]. Such predictions may further translate neuroimaging research into clinical practice [105,106]. The adoption of ML approaches is determined by multiple factors including the prediction task, the sample size and the nature of the input features [63]. With well-defined goals, supervised learning algorithms are adopted to attain the goal of making predictions as opposed to disentangling the underlying causal sources of rs-fMRI data [63]. SVM, a high-complexity model, is selected to maximize the classification performance and test the hypothesis that such partial sleep deprivation state could be successfully deducted from rs-FC and establish the possibility of such "diagnostic tool" [63]. This study will thus extend prior sleep deprivation research by applying SVM to classify rs-fMRI features exemplified by sleep state (sleep deprived/well-rested) with a secondary analysis of the Stockholm Sleepy Brain study dataset.

Multiple merits to this valuable dataset deem it suitable for secondary data analyses. The sleep manipulation achieved high ecological validity by 1) allowing participants to sleep in a naturalistic home environment with ambulatory polysomnography (PSG) and 2) delaying bedtime to three hour prior to typical waketime. Three hour meets the threshold of <4 hour of total sleep time as it would induce evident effects on physiological and subjective sleepiness [107]. Partial sleep deprivation, or sleep restriction, is more common in everyday life yet much

understudied compared to total sleep deprivation [108]. Compared to total sleep deprivation, experimentally induced partial sleep deprivation is a more ecologically valid condition given the widespread effects of sleep loss through chronic sleep restriction and sleep fragmentation [109]. Functional imaging studies of partial sleep deprivation are well poised to investigate perturbed and compensatory brain network dynamics in a reversible manner [40]. Nilsonne and colleagues also suggested that compared to total sleep deprivation, partial sleep deprivation would lower the chance of participants falling asleep during the experiment [104]. During rs-scans, participants were instructed to look at a fixation cross and were monitored by eye-tracking. Only once did one participant's eye-closure last for more than five seconds, and the MRI operator spoke a wake-up call through the participant's headphone. In addition to two eight-minute rs-scans per session, the participants also provided subjective sleepiness ratings during the latter of the rs-scans and completed psychomotor vigilance task (PVT) as a psychomotor measure of vigilance. The data collected from both young and senior adults may reveal the moderating effect of age on the influence of sleep deprivation.

The present study assesses the ability to classify the acute partial sleep deprivation state by applying a SVM classifier on a set of pre-determined features derived from rs-fMRI data with combined methods. Feature reduction is considered a fundamental process before applying predictive models [81]. This step can remove redundant features and noise, thus improving prediction accuracy, generalization, and interpretability of the models [81]. Several feature reduction/selection approaches exist, including applying supervised data-driven techniques as multivariate wrappers as recursive forward selection and feature elimination [63]. In this study, the authors constructed a focused feature set with existing domain knowledge [63] from meta-analyses (activation likelihood estimation) of sleep deprivation rs-fMRI datasets and seminal sleep

deprivation studies [68,101,110–114]. The dataset featured a within-subject design comprising of well-rested and sleep-deprived conditions. The experimental conditions are regarded as the ground truth to compare and evaluate the classification scheme. This approach compares the accuracies of multiple previously found sleep-deprivation-related rs-fMRI FC parameters (i.e., selected features). Thus, it will help elucidate whether these *a priori* selected features based on existing literature can inform ML based classification of acute partial sleep-deprivation-related rs brain activity.

II: Methods

Study design and participants

The database for the present analyses was retrieved from the Stockholm Sleepy Brain Study (https://openneuro.org/datasets/ds000201/versions/1.0.3) [115]. The following description of the study design, participants and data collection was abbreviated from manuscripts on the same dataset [104,116]. The rs-fMRI dataset was derived from the participation of 86 naïve and healthy (e.g., no present or past psychiatric or neurological disorders) participants, including 39 senior adults (M_{age} = 68.8, $Range_{age}$ = 65-75 years) and 47 young adults (M_{age} = 23.5, $Range_{age}$ = 20-30 years). The study featured a crossover within-group design: in a counterbalanced order with an interval of approximately one month between sessions, all participants were randomized to complete one full sleep session in which they maintained their typical bed and wake time, and one sleep deprivation session, during which they delayed their bedtime to only sleep for three hours. The rs-fMRI scans happened in the evening (approximately between 18:00 and 21:00 to reduce confounding effects from diurnal variability and circadian rhythms [117,118]] following each sleep condition, with the experimenters at the MRI scanner blinded to participants' sleep condition. The Stockholm Sleepy Brain Study was preregistered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02000076) and was approved by the Regional Ethics Review Board of Stockholm (2012/1870–32). Participants provided written informed consent and experiments were performed in accordance with the Declaration of Helsinki and applicable local regulations.

Experimental tasks and MRI acquisition

Two eight-minute rs-scans were acquired during each session. The first noninterrupted rs-scan occurred at the beginning of the session, after a four-minute anatomical scan; the second rs-

scan took place at the end of the session, following approximately one hour of tasks with emotional stimuli. During the rs-scans, participants were instructed to look at a fixation cross on a gray background, presented using goggles. Duirng the second scan only, participants were instructed to rate their sleepiness every two minutes with the single-question 9-point Karolinska Sleepiness Scale (KSS) [119]. Participants were also monitored by eye-tracking for vigilance and only one participant was given a wake-up call through the participant's headphone as their eye-closures lasted for more than five seconds. A General Electric Discovery 3T MRI scanner was used to acquire the Echo-planar images with the following parameters: flip angle 75◦, TE 30, TR 2.5 seconds, field of view 28.8 cm, slice thickness three mm, 49 slices; T1-weighted structural scans were acquired with a sagittal BRAVO sequence, 24 cm field of view, and one mm slice thickness.

MRI data processing and analysis

Results included in this manuscript came from preprocessing performed using *fMRIPrep* 22.0.2 [120,121] (RRID:SCR_016216), which is based on *Nipype*1.8.5 [122,123] (RRID:SCR_002502).

Preprocessing of B_0 inhomogeneity mappings

A total of two fieldmaps were found available within the input BIDS structure for this dataset. A B_0 nonuniformity map (or *fieldmap*) was estimated from the phase-drift map(s) measure with two consecutive GRE (gradient-recalled echo) acquisitions. The corresponding phase-map(s) were phase-unwrapped with `prelude` (FSL 6.0.5.1:57b01774).

Anatomical data preprocessing

A total of 2 T1-weighted (T1w) images were found within the input BIDS dataset. All of them were corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` [124],

distributed with ANTs 2.3.3 [125] (RRID:SCR_004757). The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), WM and GM was performed on the brain-extracted T1w using `fast` (FSL 6.0.5.1:57b01774, RRID:SCR_002823) [126]. A T1w-reference map was computed after registration of 2 T1w images (after INU-correction) using `mri_robust_template` (FreeSurfer 7.2.0) [127]. Brain surfaces were reconstructed using `recon-all` (FreeSurfer 7.2.0, RRID:SCR_001847) [128], and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical GM of Mindboggle (RRID:SCR_002438) [129]. Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [130] (RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration* [131] *Model* (RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing

For each of the 4 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using `mcflirt` (FSL

6.0.5.1:57b01774) [132]. The estimated *fieldmap* was then aligned with rigid-registration to the target EPI (echo-planar imaging) reference run. The field coefficients were mapped on to the reference EPI using the transform. BOLD runs were slice-time corrected to 1.22s (0.5 of slice acquisition range 0s-2.45s) using `3dTshift` from AFNI [133] (RRID:SCR_005927). The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration [134]. Co-registration was configured with six degrees of freedom. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions) [135] and Jenkinson (relative root mean square displacement between affines) [132]. FD and DVARS were calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power [135]). The three global signals were extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*) [136]. Principal components were estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components were then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM, and combined CSF+WM) were generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, a mask of pixels that likely contain a volume fraction of GM is subtracted from the aCompCor masks. This mask was obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks were resampled

into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components were also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values were retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components were dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each [137]. Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. Additional nuisance timeseries were calculated by means of principal components analysis (PCA) of the signal found within a thin band (*crown*) of voxels around the edge of the brain, as proposed by [138]. The BOLD time-series was resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. Many internal operations of *fMRIPrep* use *Nilearn* 0.9.1 (RRID:SCR_001362) [139], mostly within the functional processing workflow.

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Functional data denoising

Because rs-fMRI data are prominently and structurally impacted by head motion and respiration, both censoring and global signal regression are strongly recommended for each source of artifact respectively [140]. Specifically, censoring is one of the most effective ways to

eliminate motion artifact and outperforms despiking and pseudocensoring with high-dimensional independent component analysis (ICA) routines [140,141]. Explicit removal of global signals or regression of PCA components of the WM is the only well-documented way to remove respiratory signals [140]. Motion censoring regressors have been applied with FD cut-off at 0.5 mm [142]. This cut-off was adopted because the lower threshold of 0.2 mm could lose substantial amount of data for some subjects, while the slightly higher cut-off at 0.5 mm has been proved to be efficient, leading to the lowest percentage of lost degrees of freedom and reaching low edge activity ratings [143].

Denoising and connectivity computation were conducted in the CONN toolbox (version 21.a). The fMRIPrep preprocessed dataset was spatially smoothed with a 6 × 6 × 6 mm kernel and further denoised with CONN's default denoising workflow [144]. Linear regression was applied with fMRIPrep to identify potential confounding factors and the temporal band-pass filtering removed temporal frequencies below .008Hz or above .09Hz [144].

To identify potential outlier subjects or runs within a study, the relative Quality Control (QC) values compared to other subjects or runs carry the most useful information [145]. Thus, applying absolute values as universal thresholds of data quality across studies may not be valid or feasible as variability will arise from the differences in acquisition parameters and preprocessing pipelines [145]. Based on subject-level QC measures, three participants' data (sub-9028, sub-9065 and sub-9079) were removed due to much higher mean motion, CSF volume or global correlation, compared to the rest of the sample. The denoising outputs were further evaluated by examining group-level QC measures: the distribution of FC values between randomly-selected pairs of points post preprocessing [144] and denoising, along with the QC-FC correlations [146]. After denoising, FC distributions reached approximately centered distributions

with reduced inter-session and inter-subject variability and a lack of noticeable QC-FC correlations.

Seed-based ROI-to-ROI connectivity metrics were generated for *a priori* selected ROIs and networks based on existing literature (Table 1). Default CONN ROI parcellation [a combination of Harvard-Oxford atlas and the automated anatomical labeling (AAL) atlas] and the default CONN network parcellation [from ICA analysis of Human Connectome Project (HCP) dataset, $N = 497$] were adopted. Given that Pearson Correlation Fisher-transformed features performed better than the ones without transformations [65], the rs-FC metrics were computed as Fisher-transformed bivariate Pearson correlation coefficients between pairs of ROI BOLD timeseries and those within selected networks. The correlation coefficients were also averaged across two runs to produce a single rs-FC matrix per session per participant.

SVM classification

Feature reduction and extraction

Based on the *a priori* selected pairs of ROIs and within and between network indexes, a total of 258 rs-FC values were present due to fine parcellations and regional overlapping among the Harvard-Oxford, AAL and CONN network parcellations. To reduce the number of features and potential redundancy and multicollinearity among the features, rs-FC values from the finer parcellations of the same broader pairs of the ROI were averaged to generate one value summarizing the ROI-to-ROI and within and between network FC. This approach eventually extracted 29 seed-based ROI-to-ROI and between and within networks FC metrics.

Several factors contribute to individual differences in FC baselines, including variations in brain morphology, normalization, vasculature and overall BOLD magnitude [147]. Given the within-subject design, two methods of centering the rs-FC values were adopted to reduce the

impact of individual baseline differences in rs-FC. The first approach was to center the within pair rs-FC values by the mean to address the paired data structure [148]. Specifically, the absolute values of the rs-FC metrics were averaged across the two conditions per participant. The rs-FC values were then divided by the means (which were always positive). The second approach is to further scale the rs-FC values by turning the continuous averaged rs-FC values (ratio values bounded by -1 and 1) into four discrete ordinal values in the following manner: if both FC values from the sleep deprivation and well-rested sessions of the same participant were positive, the larger rs-FC value (the more positive value) of the two values was labeled as .75, and the smaller rs-FC value (the less positive value) as .25. If both rs-FC values were negative, the larger FC value (the less negative value) was labeled as -.25, and the smaller FC value (the more negative value) as -.75. If the two rs-FC values differed in directions, the positive value was labeled as .25 and the negative one as -.25. This way, within each session of the same participant, the directions and relative strengths of the FC values were retained, whereas information about the individual baseline and magnitude of rs-FC changes between sleep deprivation and well-rested conditions within each session of the same participant was discarded. The continuous and ordinal values from both approaches were adopted as the features for the subsequent SVM binary classifications.

Model training and testing with nested cross-validation

The following SVM analyses with nested cross-validation were conducted according to the practical guide to support vector classification [149] and predictive modeling of individual differences in neuroimaging [150]. The senior adults' dataset was first transformed and scaled. Present theoretical and numerical investigations fail to generate a consensus on the optimal data splitting ratio (to split the dataset into a training and a testing dataset) [151]. Picard and Berk [152]

have recommended 25-50% for the testing set and common practices of training to testing ratio include 80:20 (Pareto principle,), 70:30, 2/3:1/3 [153], 60:40, and 50:50 [151,154]. The senior adults' dataset was randomly split into the training dataset (2/3 of the dataset) and the testing dataset (1/3 of the dataset) to keep the two subsets independent. Subject-wise, instead of record-wise, data splits were adopted to keep the testing dataset independent and avoid identity confounding [155]. Given the limited sample size, K-fold is the dominant cross-validation choice with K (typically 5 or 10) number of non-overlapping subsets [63]. If K equals the number of samples in the training set, this resampling procedure is Leave-One-Out (LOO) cross-validation [63]. The radial basis function (RBF) kernelized model was adopted with 10-fold cross-validation and an exhaustive grid search to tune parameters C and γ [149]. The best parameters were adopted to train the whole training dataset [149]. The trained model was tested on the independent testing dataset [149]. Lastly, the trained model was applied to the independent young adults' validation dataset. The entire SVM procedure was performed 100 times to avoid unexpected bias during the initial randomized splitting of the senior adults' dataset. Unbiased class-specific accuracy, sensitivity and specificity of the classifiers were reported. For the best performing model, precision and F1 values along with averaged confusion matrix were provided. The confusion matrix comprises information about the actual classification from the reference/actual dataset against the predicted classifications generated by SVM models. The comparisons of the SVM classifier (sleep-deprived or well-rested) with the reference data were documented by the outcomes of the confusion matrix (as in Table 2). F1 score is an overall accuracy value combining precision (false positive rate) and recall/sensitivity.

Slightly varied approaches were tested, including the adoption of linear SVM and LOO cross validation with ten repetitions. Linear SVM was adopted due to its low sensitivity to a high

dimensionality [79,81]. The analyses of the averaged FC values (without ordinal transformation) were also reported. Post hoc forced choice was implemented such that model was forced to compare against the two sessions under the same participant and label each with one session with a different condition [147]. Specifically, the predicted labels of the two sessions (sleep-deprived or well-rested) from the same participant were forced to differ, ensuring that the two sessions from a participant were not assigned the same sleep condition. Within the same participant, one session was assigned the label with a higher probability value of either predicted condition (sleep-deprived or well-rested), leaving the other session to be assigned with the left-over label. All SVM analyses were conducted with the splitTools package to randomly subject-wise split the senior adults' dataset into training and testing sub-datasets and with the e1071 package (v1.7-13) [156] to perform the analyses in R (v4.2.1) [157]. The entire reproducible analytic script and dataset are available in an online repository. A general flowchart is provided to summarize the method section (Figure 1).

III: Results

Participant and dataset characteristics

The sample included in this secondary analysis consisted of 75 participants' scan data from both sessions. There were 34 (18 identified as female) senior adult participants (age 65-75 years) and 41 (21 identified as female) young adult participants (age 20-30 years). A total of eleven participants' data were excluded [sub-9078 (young, female) without fMRI data; sub-9028 (young, male), sub-9065 (senior, male), and sub-9079 (senior, male) due to significant QA index outliers; sub-9016 (young, male), sub-9022 (young, female), sub-9044 (young, male), sub-9066 (young, female), and sub-9095 (senior, male) with only one session; sub-9029 (senior, female) without the second rs scan during the first session and sub-9025 (senior, female) without the second rs scans during both sessions]. The sleep manipulation was mostly successful based on PSG, sleep diary data and self-reported KSS ratings (see [104,116,158] for detail). Consistent with previous reports [104], no significant group differences in the number of volumes above the FD threshold were identified between conditions (sleep deprived and well-rested) or age groups (senior and young). The dataset was fully balanced (i.e., an equal number of sleep deprivation and well-rested conditions) and all subsets of the datasets (training, testing and validation datasets) were also balanced.

Model discriminative ability

Models trained on senior adult dataset

The discriminative ability of the SVM models trained on senior adult dataset was shown in Table 3. Compared with models with non-transformed dataset, the models with transformed datasets (to reduce the impact of individual baseline differences) showed higher classification accuracies. The performance of the models with the ordinal transformed dataset displayed above

chance (50%) potential to differentiate between the sleep deprivation and well-rested states based on information embedded in the FC values within the 29 *a priori* selected regions and within and between the networks. All models showed similar levels of sensitivity and specificity, suggesting balanced performance in identifying true positives and true negatives. In general, RBF models with LOO cross-validation appeared to slightly outperform linear models. The best model (RBF kernel, LOO with transformed dataset) displayed 68% precision, 66% recall and an F1 score of .65. Post hoc forced choice adaptation did not consistently improve the prediction accuracy of the best performing model.

The overall validation diagonal accuracy (around 54%) of the trained models on senior adult participants' dataset on young adult participants' dataset suggested that the models mostly randomly categorized the two sleep conditions in the validation dataset. Thus, information learned from senior participants' dataset did not enhance the model's ability to differentiate between the sleep deprived and well-rested conditions within the young adult participants' dataset.

Models trained on young adult dataset

The discriminative ability of the SVM models trained on young adult dataset was shown in Table 4. Compared with models with non-transformed dataset, the models with transformed datasets (to reduce the impact of individual baseline differences) showed higher classification accuracies. All models showed close to chance ratio to classify the sleep condition. Meanwhile, models with the ordinal transformed dataset displayed highest levels of sensitivity and specificity, with slightly better performance in identifying true positives than true negatives. The overall validation diagonal accuracy of the trained models on young adult dataset were close to chance level. This may indicate that information gained from differentiating young adult

participants' sleep states did not extend to distinguishing the sleep deprived and well-rested conditions within the senior adult participants' sleep states.

IV: Discussion

In this secondary data analysis, it was examined if systematic perturbations to the intrinsic FC will occur post one night of partial sleep deprivation among a sample of healthy senior and young adult participants. To assess the extent of such changes, SVM models were applied to binarily classify the labels of the sleep conditions (sleep deprived or well-rested) with the participants' rsfMRI dataset. The features selected were the rs-FC metrics among *a priori* selected list of ROIs and networks based on existing literature. These features were further transformed to reduce redundancy and the impact of individual differences in baseline rs-FC. Among various models trained on senior adult dataset, the RBF kernelized SVM model with LOO cross-validation performed best (around 68% accuracy rate) in predicting and differentiating the sleep deprived and well-rested states within the senior adult participants in the sample. In contrast, all models trained on young adult dataset achieved close to chance overall accuracy rate. The above chance labeling accuracy of the tested algorithms (trained on senior adult dataset) with 63% sensitivity and 68% specificity could be interpreted as modest evidence indicating the presence and magnitude of acute partial sleep deprivation induced systematic perturbations to the intrinsic human neural FC, especially among senior adults. To test if the patterns embedded in the rs-FC differences between sleep deprived and well-rested conditions in either the senior adult or young adult datasets, which were picked up by the models, could be generalized to the dataset of the other age group, the models trained were validated with the other age group's dataset. The near chance validation classification accuracy suggested lower differentiating power in the trained models and hence, probably indicating different compensatory and non-compensatory sleep deprivation-induced connectivity alterations between the samples of the young and senior adults. The following discussion is devoted to speculations

on the developmental differences in sleep deprivation induced neural alterations, a detailed examination of the potential limitations of the present approach to offer insights and recommendations for future investigations, along with considerations of the clinical application.

Are senior adults more vulnerable to sleep deprivation than young adults?

In the present study, senior adults' sleep states were classified with higher accuracy than young adults' sleep states and the models trained on either age group performed poorly on the other age group in external validations. This suggested that a consistent pattern of rs-FC alterations may have been identified in the senior adult dataset, yet not in the young adult dataset. In addition, the rs-FC alterations experienced by the senior adults may not be present among the young adults. This may indicate that in contrast to senior adults in this study, 1). young adults could be more resilient to acute partial sleep deprivation such that the rs-FC integrity was not perturbed, 2). Larger individual variations in rs-FC responses to acute partial sleep deprivation were present among young adults, 3). Young adults were already in a state of chronic sleep insufficiency, and/or 4). Other ROIs and networks apart from the a priori list of features were more impacted. In comparison, senior adults could be more responsive to acute sleep deprivation such that 1). Senior adults displayed reduced rs-FC structure integrity due to the sleep manipulation, and/or 2). Senior adults recruited more compensatory effort. Importantly, the rs-FC alterations among senior adults were not mirrored in young adults.

In general, senior adults display lower FC than young adults. Aging-related neural change could start as early as during the transition between young and middle adulthood [159]. With structural changes including white matter degeneration of vascular genesis, a disconnection model has been proposed to explain neurocognitive aging [160]. In task-based fMRI studies, healthy old adults have been found to present higher regional activation, which were interpreted

as a compensatory mechanism [161]. More recent evidence on rs-FC studies concluded that compared to young adults, senior adults exhibited both higher levels of neural activation and reduced and disrupted rs-FC, especially within the DMN [161]. Rs-FC within the sensorimotor networks has been found to mediate age-related decline in executive function [162]. With ReHo, Nilsonne et al. replicated the finding that compared to young adults, senior participants had lower connectivity within most ICA-derived rs-FC networks and within medial prefrontal cortex, superior temporal lobes and insula bilaterally [104].

It is speculated that sleep deprivation ages young adults' brain such that they resemble the elderly brain. In one study, within and between module rs-FC were compared among three groups, young participants in well-rested and sleep deprived conditions and senior participants with typical sleep [163]. Between module rs-FC in the subcortical and cerebellar networks were low in both the young sleep-deprived and senior groups [163]. Consistent with this finding, only acute total sleep loss was find to change brain morphology in an aging-like direction in young adult participants [164]. However, no studies to date directly examined the potential moderating role of age on sleep deprivation other than the analyses conducted by Nilsonne et al. [104]. With conventional group contrasts, Nilsonne and colleagues did not identify major rs-FC related interactions between age group and acute partial sleep deprivation [104]. In contrast, the present result of senior adults' sleep states being more distinguishable than young adult' and senior adults' sleep deprived pattern being non-transferrable to young adults may provide evidence that senior and young adults were differentially impacted by acute partial sleep deprivation with senior adults more susceptible to such sleep manipulation.

Is mixing and matching ideal?

The selected features adopted in the present study were rs-FC values from ***a priori* selected list** of pairs of ROIs and networks. The list was derived from the accumulation of published findings built on conventional explanatory approaches focusing on statistically significant group level differences. The selected features based on the list were then used to train, test, and validate SVM models, which aimed at predicting individual inferences. Hence a mixing and matching approach was adopted. Despite the widespread application of using the results of group differences to select features for the classification, this practice is discouraged: 1) it is considered double dipping as any use of test samples in any part of the training (including feature extraction, selection and classifier training) poses a bias and leads to inflated results [165,166]; 2) variables based on significance and prediction approaches may possess different properties of their underlying distribution analyses [94] and discarding features based on group mean-based results that meet the statistical threshold could lose valuable discriminatory information [87]. The first concern may not apply to the present study as feature selection was not directly based on group differences in the same dataset; in fact, Nilsonne et al. found no statistically significant group level differences with similar FC metrics [104]. The second concern could be partially contributing to the sub-optimal performance of the SVM models due to non-optimized selection of features. Hence, supervised and unsupervised selection approaches as filtering and wrapper methods are recommended [87]. Additional feature extraction and selection approaches could be adopted in future studies, including input dimensionality reduction (PCA, locally linear embeddings), supervised data-driven techniques as multivariate wrappers as recursive forward selection and feature elimination. These steps could be applied with the full rs-FC matrix instead of the same *a priori* selected list in this present study.

The rs-FC features available could be further expanded to include more variables within the list of **rs-FC metrics** (seed-based, ROI-to-ROI, network-based, graph theoretical, and dynamic connectivity measures) [144]. Voxel-based physiological (VBP) variables as ALFF, Fractional Amplitude of Low-Frequency Fluctuations (fALFF) and ReHo could also be adopted as they provide complementary information (i.e., variability of the BOLD signal within the stand frequency window) to scale invariant correlation-based metrics [144]. Rs-hemodynamic and metabolic correspondence with positron emission tomography (PET) suggests that ALFF spatially correlates with the blood volume whereas fALFF and ReHo spatially correlate with metabolic rate of glucose [167]. For instance, acute total sleep deprivation reduces ALFF in DMN and frontal-parietal network nodes and increases ALFF in the bilateral thalamus, motor cortex and visual cortex [168]. Sustained attentional impairment post sleep deprivation is predicted by increased ALFF in the visual cortex, frontal-visual connectivity, and decreased frontal-thalamus connectivity [168]. Hence, each metric emphasizes a different approach to defining neural connectivity and the present ROI-to-ROI and network-based metrics are limited.

Similarly, different **analysis methods** are also complementary, and applying several methods to the same dataset may yield better results and aid the interpretation of the common/divergent findings [169]. In addition to SVM, embedded techniques as LASSO and Elastic net could also be tested; such models may combine the advantages of both filter and wrapper models by integrating feature selection into the learning algorithm, and enhance the interpretability of the model and thus probe the relationship between the labels and the features [63]. The feature selection model adopted in the present study assumes the features are flat, thus independent [170], whereas intrinsic structures exist in the rs-FC. Hence, feature selection algorithms for structured features (group, tree, or graph structure) need to be tested as well [170].

Moreover, FC networks can be heterogeneous. For instance, the frontoparietal network, has been found to be, rather than a unitary domain general system, containing a fine-grained internal organization, associated differentially with DMN and DAN [171]. Much of the rs-FC literature utilized *a priori* seed regions and ROI analyses and such constrained analyses can overlook key connectivity patterns that exist outside of typical networks [172]. While the aforementioned ML classification models follow a backward route, which starts with the ground truth (condition labels), a recent addition to the conventional forward route (group level analysis), fc-MVPA analysis is another valuable candidate to explore [173]. To this date, no study has applied fc-MVPA to compare the accuracies of the models with features extracted from various rs-fMRI connectivity models to classify well-rested and sleep-deprived states. Whole-brain fc-MVPA could be impactful as ROI based analysis is limited in statistical power and cannot provide detailed results as whole-brain analysis with multiple corrections [174]. As each method emphasizes different approaches to defining and analyzing rs-fMRI activity and FC, there is no single method regarded a golden criterion standard on its own. Since different rs-fMRI analysis methods are complementary, applying several and combined methods to the same dataset may yield more complete data-driven characterization of rs-FC [169] post acute partial sleep deprivation.

The linear and kernelized SVM models adopted in the present study along with logistic regression with penalty (L1, L2, and Elastic net) are suitable for limited **sample sizes** and can reduce the issue of overfitting. Sample sizes needed for ML models depend on the type and complexity of the models [63]. Hence, successful testing of other ML models needs to address the most limiting factor in the application of ML in neuroimaging studies -- the limited sample size [87]. Studies of limited sample sizes utilizing idiosyncratic rs-fMRI analysis methods/features are dominant in the existing literature on sleep-deprivation. Large training data sets increase

classification accuracy [175,176], whereas small thus unrepresentative samples reduce the generalizability of the results [87]. The sample size of the present age group-based analysis is relatively smaller than those reported in the key total sleep deprivation studies with young adults, which may lead to overestimation of the performance of the models due to the limited availability of training data. Decentralizing and data sharing are essential to the growth in this field [87]. Network analysis of cross-site rs-fMRI data pre and post sleep deprivation could effectively resolve the challenges with limited sample size and allow the application of more data-intensive ML methods (as neural-network based approaches).

In addition to nested cross-validation and permutation tests, False Discovery Rate correction can be applied to correct for multiple model and parameter comparisons [150]. The relationship between sensitivity and specificity of the classification models can be further characterized with a receiver operating characteristic curve [177] and quantify the overall model performance as the area under the curve [178] to determine an optimal cut point with largest number of true positives and negatives [150,179]. These future efforts can compare the classification accuracy and interpretability of various ML models, and further suggest which feature(s) serve(s) as the most suitable basis for ML based classification of acute-partial-sleep-deprivation-related brain activity and the pros and cons of different ML models in pursuing related research questions.

A comprehensive systematic review and meta-analysis of MLC of Autism Spectrum Disorder diagnoses with rs-fMRI data concluded that AAL116 seems a preferred **atlas** [65]. Atlases could be selected arbitrarily in the rs-fMRI community, and given significant variability in classification from varied atlases, finding an optimal atlas for classification might be infeasible [180]. It is suggested that ensemble models that average across parcellation schemes should be used

instead of individual atlas-based models [180]. In the present study, CONN's default (Harvard Oxford, AAL and HCP) atlases were used and due to the existing parcellation, multiple overlapping pairs of ROI-to-ROI and within and between network FC values were averaged to create a single rs-FC value as one feature, to reduce the number of features and potential redundancy and multicollinearity. For instance, the entire cerebellum is finely parcellated into 18 smaller regions in CONN's default atlases, thus creating many pairwise FC with bilateral IPS. The approach adopted in this study averaged all these FCs to generate one FC to summarize the FC between IPS and cerebellum. Meanwhile, averaging across pairs of ROI FCs fails to appropriately weight each original FC value based on voxel numbers included to compute the original FC value. In future, a combination of appropriate parcellation atlas and straight-forward ROI masking could be used to avoid averaging fine-grained FC values originating from the same/overlapping region(s). Schaefer et al.'s atlas with a Markov Random Field model [181] could also be adopted instead of a boundary based or clustering derived atlas due to its superior homogeneity [180].

Another area of improvement is to enhance rs-fMRI **dataset validity** and reduce noise. Although motion did not significantly differ between the age groups or sleep conditions in the present dataset [104], no denoising approaches will fully account for motion-related artifacts in FC estimates [182]. Based on comprehensive comparisons of rs-fMRI denoising approaches, Independent Component Analysis based strategy for Automatic Removal of Motion Artifacts (ICA-AROMA) [183] is recommended as a preferred rs-fMRI pre-processing technique for teenager and adult participants [182,184], whereas aggressive ICA-AROMA is likely the most suitable denoising technique for senior adult participants [143], which is consistent with a U-shaped curve of head motion over the lifespan [185]. In the present study, both scrubbing and the

regression of noise components from WM and CSF were applied [144]. Although PCA WM component regression could equate the effect of global signal removal, it may not completely eliminate respiratory artifacts embedded in the averaged global rs-BOLD signal [140]. However, the contentious application of global signal removal in sleep deprivation related rs-fMRI analyses is discouraged due to its propensity to produce artificial deactivations [143,186,187] and obscure sleep deprivation altered global signal modulations [101]. Hence sensitivity analyses with and without global signal regression should be contrasted. The combination of global denoising and spatial denoising could further remove artifacts [188]. In the current analysis, the rs-FC matrixes from two runs were averaged to create one rs-FC matrix per session per participant. The rs-scan at the beginning of the scan session could be a more reliable representation of the baseline rs-FC as prior task performance may impact the rs-data and several minutes may be required for brain physiology measures (endogenous low frequency oscillatory dynamics and regional cerebral blood flow) to recover to baseline [189,190]. Lastly, even though Nilsonne and colleagues designed excellent protocols to monitor and keep the participants alert during the rs-scans (pupillometry and wake-up calls), micro episodes of sleep intrusion could happen [104]. Rolling window detection of sleep intrusions (RoWDI) may be applied to detect sleep intrusion during post sleep deprivation rs-fMRI session [191] as the characterization of FC within a sleep deprived brain may reasonably include such brief transitions between awake and sleep states.

Most studies favor one data type without combining and integrating **modalities**, thus missing important changes which could only be partially detected by each modality [192]. Multimodal fusion provides a more comprehensive description of altered brain patterns and connectivity, hence, it should be utilized more in answering scientifically and clinically relevant questions [87]. The combination of other neural methodologies including pupillometry [193] and PSG,

and transfer-learning from the cognitive and affective fMRI tasks in the valuable Stockholm Sleepy Brain study dataset could a reveal more complete picture of acute partial sleep deprivation induced transient neural changes.

To what extent is the sleep-deprivation and well-rested states in this partial sleep deprivation dataset truly separable?

Another explanation to the sub-optimal performance of the models is that the impact to FC from one night of partial sleep deprivation among healthy participants could be minor. The *a priori* selected ROIs and networks were based on total sleep deprivation rs-fMRI literature, with potentially low applicability to the study of one night of partial sleep deprivation. Nilsonne et al.'s original conclusion that acute partial sleep deprivation failed to cause statistically significant rs-FC group differences (intra and inter FC within DMN, task-positive network or other indexes as ReHo, ALFF) other than the increased global signal variability [104] incentivized the adoption of MLC in the present study. Relatedly, a well-trained brain age ML model analyzing T1 MRI data revealed that whereas acute total sleep deprivation temporarily increased human brain age by one to two years, this effect was not strong enough to be detected in acute (three hour time-in-bed for one night) or chronic partial sleep restriction (five hour time-in-bed for five continuous nights) conditions [164]. This might indicate that partial sleep restriction, unlike total sleep restriction, tends to induce minor brain morphologic changes [164]. The null results in Nilsonne et al.'s study and the sub-optimal MLC accuracy in the present study beg more fascinating research questions: are these results due to the fact that neurophysiological and behavioral compensations are adaptive enough to handle partial sleep deprivation? If not three hours of sleep, what is the reliable threshold of partial sleep deprivation that truly burdens the integrity of rs-FC? Would there be rs-FC differences depending on the stage of sleep deprivation (REM or Non-REM)?

The scans in the present dataset were all performed around a similar **time** during the evening, which is important for accounting for the impact of regular diurnal variability on sleep deprivation [1]. However, changes in FC could occur within hours of prolonged wakefulness [118,194]. This is consistent with the rs-FC changes examined by Kaufmann et al.'s study [1]. In the study, rs-scans were collected at three consecutive time points (Day 1 morning after normal sleep, Day 1 evening after a regular day of waking, Day 2 next morning of total sleep deprivation or normal sleep). The classification analysis of the rs-FC values collected on Day 2 morning post sleep deprivation was much more similar to that of Day 1 night prior to sleep deprivation than that of Day 1 morning [1]. Hence, the design of evening scan time in the Stockholm Sleepy Brain study might dampen the (already subtle) differences in rs-FC between well-rested and partial acute sleep deprived conditions.

In addition to the possibility of minor partial sleep deprivation induced rs-FC alterations, the changes to rs-FC post acute partial sleep deprivation could be highly heterogeneous among the participants. The near chance validation result from the senior adults' dataset trained models on young adults' data may hint at the presence of multiple **moderators**. For instance, large inter-individual differences in sleep deprivation-induced cognitive impairment exist [195]. Specifically, phenotypic and heritable individual differences exist in the type [196] and extent of vulnerability to sleep-deprivation-induced impairment across multiple domains including three probable orthogonal dimensions: self-evaluation of sleepiness, fatigue and affect, cognitive processing (working memory, mathematical processing) and behavioral alertness (psychomotor sustained attention) domains [197,198]. In one study [99], participants with high vulnerability to sleep deprivation were first selected to study the sleep-deprivation-induced perturbation to neural networks. Similarly, in the next step of the present study, behavioral alertness (indexed by PVT

performance decline) and self-evaluation of sleepiness (measured by significantly elevated subjective levels of sleepiness) could be inspected to identify a subset of the participants who exhibited and experienced evident functional impairment from the acute partial sleep deprivation manipulation. Both criteria are important as subjective sleepiness and objective PVT performance decline may be separate constructs and reflected in different FC alterations post sleep deprivation [199]. Zooming in on this subset of participants may allow the classification model to differentiate between the sleep-deprived and well-rested states with higher accuracy as the neural underpinnings underlying the two states would be factually more separable compared to the analysis including the participants who are relatively resilient to the negative impact of acute partial sleep deprivation.

The **PVT** is a well-established paradigm testing reaction times to a cue occurring at random inter-stimulus intervals [24]. It has become a gold standard for examining the impact of circadian rhythmicity and homeostatic sleep pressure on neural responses [200,201]. Evidence includes that stronger anti-correlations among on and off task networks during rested wakefulness may predict on individuals' PVT performance post sleep deprivation [101]. Sleep deprivation also leads to dynamic FC [67] and small-world network changes [202] which were correlated with PVT performance. Lapses during the PVT, defined as reaction times exceeding 500ms or slower than twice the mean of the rested wakefulness reaction time, are widely used to index cognitive instability post sleep deprivation [101] with high ecological validity. Medical errors, adverse events, serious industrial and transportation accidents, could happen during these sleep deprivation-induced brief cognitive/attention lapses [203,204]. These individual differences in cognitive instability and vulnerability to sleep deprivation appear trait-like [197,198]. Trait-like post-sleep deprivation cognitive instability measured by PVT lapses is linked with low levels of WM

microstructural integrity (i.e., fractional anisotropy) of the upper longitudinal tract fibers connecting the frontal and parietal lobes (the superior longitudinal fasciculus and the splenium of the corpus callosum) [174]. One explanation is that stronger structural connectivity in these WM tracts might support the speed of electrical signal transmission in the thalamus thus reducing sleep pressure induced attention lapses [174,205]. PVT lapses have also been associated with activations in the frontoparietal regions, extrastriate visual cortex and thalamus [206]. Hence in future subset analyses, trait-like individual differences in vulnerability to sleep deprivation could be defined with PVT median split of lapses to categorize participants as vulnerable or resistant to acute partial sleep deprivation [101,174].

Lastly, **individual differences in baseline rs-FC** could further contribute to the suboptimal classification accuracy rate in the present paired-design study. If the trained models mostly rely on the magnitude of rs-FC to distinguish the conditions, both sessions of a test participant could be classified as sleep-deprived or well-rested. In the present study, two different methods were applied to reduce the impact of individual differences. The ordinal transformation approach outperformed the mean-centering approach. In the best model with ordinal transformation, only information as the rs-FC direction (positive or negative) and the relative size (larger or smaller FC values) was extracted, turning continuous/ratio FC values into discrete/ordinal values. Even though the ordinal transformation method improved the classification accuracy from 55% to 68%, nuanced and potentially valuable information embedded in the magnitude of the rs-FC values was dichotomized, rendering some differences exaggerated and some differences minimized. Hence, a more effective way of accounting for individual differences in baseline rs-FC could further improve the classification performance of the model. Another approach is to retain the subject ID information in the model and force the

model to compare against the two sessions under the same ID and label each with one different condition [147]. This strategy could shed light on the valuable rs-FC features in distinguishing the sleep conditions in the same participant, however, the model may not be necessarily generalizable across the population. At this point, even though sessions from the same participants were always included in the same subset of training or testing dataset and the dataset was completely balanced, the models trained in the present study were not informed/instructed to classify the two sessions from the same participant with different conditions. Although a post-hoc forced choice adaptation in the testing step was applied to the best performing model, this approach did not consistently improve the classification accuracy. This post-hoc forced choice adaptation only took place during the testing step could render this adaptation less effective or ideal because the trained model did not take advantage of this piece of new information during model tuning and training steps. Therefore, the 68% accuracy rate of the present binary classification models could be further improved with force choice applied throughout the ML process.

Clinical implications and applications of present findings

Studying rs-FC alterations from acute partial sleep deprivation can inform the public about the strong brain-behavior connection, and potentially motivate individuals to reduce bedtime procrastination and the negative sleep outcomes [207]. Addressing sleep health is key to achieving health equity [16]. Given that most studies adopted the acute total sleep manipulation, the limited and inconsistent findings on how partial acute sleep deprivation impacts young and senior adults further reveals the current inadequacies of knowledge regarding the sleep-deprived human mind. Knowledge to be gained from partial sleep deprivation studies is critical as chronic partial sleep deprivation is the dominant contributor to sleep insufficiency. The present finding

on altered rs-FC could be a direct consequence of deprivation or due to compensation of deprivation, e.g., increased effort to maintain vigilance [1]. It may also hint at how the brain networks may later recover from acute sleep curtailment. Like most basic scientific findings on sleep loss, the present finding on altered rs-FC post acute partial sleep deprivation will not be directly and spontaneously transformed into knowledge to be routinely applied in the clinic. Nevertheless, the possible differential impact of acute partial sleep deprivation among senior and young adults could still highlight the global impact of sleep insufficiency on human brain and emphasize the importance of addressing sleep insufficiency and effectively coping with nights of curtailed sleep, especially among the elderly population. Identifying these rs-FC alterations from acute partial sleep deprivation can potentially motivate individuals to reduce bedtime procrastination and the negative sleep outcomes [207] and inform the public about the strong brain-behavior connection.

Addressing sleep health is key to achieving health equity [16]. Sleep insufficiency and related abnormalities are robustly observed across all levels (etiology, diagnosis, therapy, and prevention) of major disorders of the brain (neurological and psychiatric) [32]. Collaborative work between the field of basic and clinical science is needed to identify, interpret, and translate findings from sleep deprivation neuroscience research. Such effort will benefit sleep health among individuals within professional circumstances of rife sleep privation (e.g., the military, aviation, transportation, and medicine) and in subtler forms including social jetlag [32] and early (middle and high) school time. As Krause and colleagues elegantly put, sleep deprivation research has "perhaps never been more pressing considering the professional, societal and clinical implications that continue to scale in lockstep with the precipitous decline in sleep duration throughout industrialized nations [32]."

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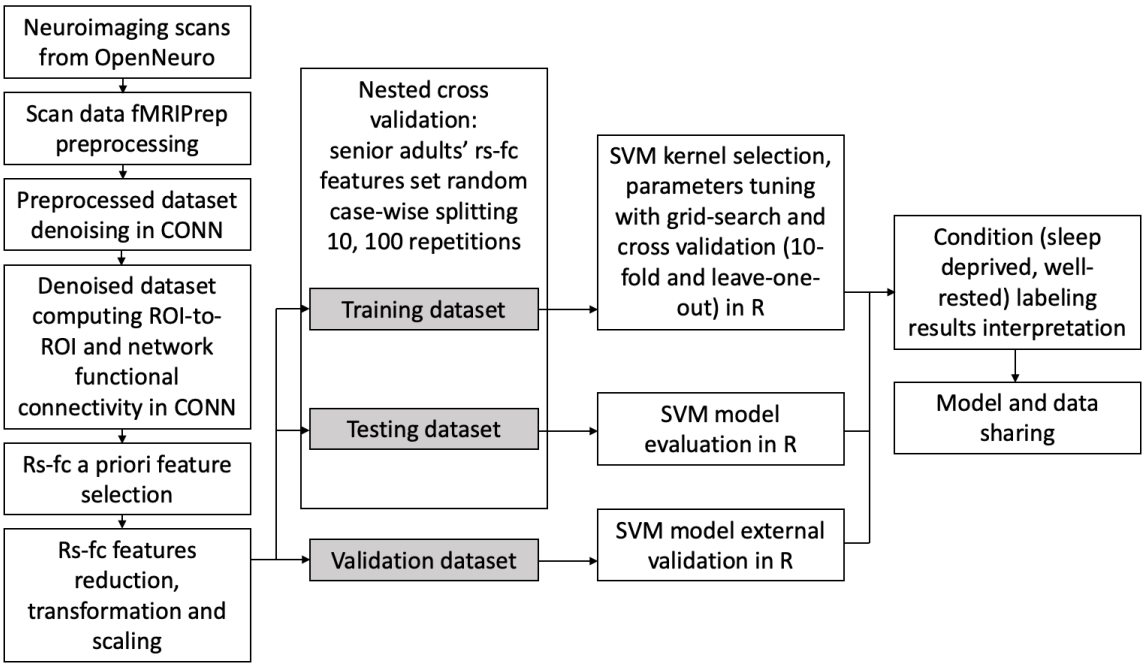
Disclosure Statement

None declared.

APPENDIX B: LIST OF SCHEMES

Figure 1

The Flowchart of Developing SVM-Based Classification Models



APPENDIX B: LIST OF TABLES

Table 1

A Priori Determined Set of 29 rs-FC Features Based on Rs-fMRI Sleep Deprivation Literature

ROI	Paired ROI(s)	Within ROI/network
r-inferior parietal lobule (IPL)	l-precuneus, l-fusiform gyrus, l-cluster of middle temporal gyrus, l-inferior temporal gyrus	r-IPL, l-precuneus/PCC
l-inferior parietal lobule (IPL)	r-cluster of IPL, superior temporal gyrus	DMN DAN SAN
bilateral amygdala	dorsal-lateral PFC, r-dorsal ACC, r-IFG, rostral ACC, r-precentral gyrus, precuneus, r-parahippocampal gyrus, r-dorsal PCC, l-PCC	
		Between networks
r-amygdala	r-mPFC	DMN & SAN DMN & DAN DAN & SAN

IPS	SPL, insula, thalamus, cerebellum, IFG, precentral gyrus, caudal & dorsal lateral occipital cortex

Note. The rs-fc features were extracted from the results in the following studies [68,101,110–114].

Table 2

The Confusion Matrix for Computing Class-Specific Accuracy

		Reference data	
		Sleep-deprived	Well-rested
Classified data	Sleep-deprived	TP	FP
	Well-rested	FN	TN

Note. True positive (TP): The number of sessions that were correctly classified in the sleep deprived condition. False positive (FP): The number of sessions that were incorrectly classified in the sleep deprived condition. False negative (FN): The number of sessions that were incorrectly classified in well-rested condition. True negative (TN): The number of sessions that were correctly classified in well-rested condition. These values were used to compute the two measures of class-specific accuracy -- sensitivity and specificity [208].

Table 3

A Summary of the Performance of SVM-Based Models Trained on Senior Adult Participants

Model	Sensitivity	Specificity	Diag	Kappa	Rand	Crand	Validation diag	Cross-validation	Repetition times
RBF (transformed_mean_center)	.59 [.25, .83]	.58 [.17, .92]	.60 [.25, .86]	.20 [-.50, .73]	.53 [.48, .75]	.06 [-.05, .51]	.51 [.39, .61]	10-fold	100
	.58 [.42, .75]	.53 [.33, .75]	.56 [.42, .75]	.13 [-.17, .5]	.51 [.48, .61]	.02 [-.04, .22]	.53 [.46, .57]	LOO	10
Linear (transformed_mean_center)	.61 [.25, .92]	.62 [.33, .92]	.63 [.32, .86]	.27 [-.36, .73]	.55 [.48, .75]	.09 [-.05, .51]	.50 [.40, .65]	10-fold	100
	.60 [.42, .83]	.60 [.50, .75]	.61 [.46, .79]	.22 [-.08, .58]	.53 [.48, .66]	.05 [-.05, .31]	.49 [.35, .60]	LOO	10
RBF (transformed_ordinal)	63 [.33, .92]	.60 [.25, .92]	.63 [.33, .92]	.26 [-.33, .83]	.53 [.48, .84]	.06 [-.05, .68]	.55 [.43, .68]	10-fold	100

	.63 [.50, .83]	.68 [.42, .83]	.68 [.55, .82]	.35 [.09, .64]	.56 [.48, .69]	.11 [-.04, .38]	.54 [.49, .61]	LOO	10
Linear (transformed_ ordinal)	.62 [.25, .92]	.61 [.25, .83]	.64 [.32, .91]	.27 [-.36. .82]	.54 [.48, .83]	.08 [-.05, .65]	.56 [.40, .66]	10-fold	100
	.64 [.50, .75]	.64 [.50, 75]	.67 [.55, .82]	.34 [.09, .64]	.55 [.48, .69]	.09 [-.04, .38]	.56 [.49, .61]	LOO	10
RBF (non-transformed)	54 [.17, .92]	.56 [.25, .83]	.56 [.36, .75]	.13 [-.27, .50]	.50 [.48, .61]	0 [-.05, .22]	.51 [.41, .62]	10-fold	100
	.55 [.33, .75]	.53 [.17, .67]	.55 [.46, .64]	.09 [-.08, .27]	.49 [.48, .52]	-.02 [-.04, .03]	.53 [.46, .61]	LOO	10
Linear (non-transformed)	.51 [.08, .92]	.54 [.08, .83]	.54 [.29, .73]	.09 [-.42. .45]	.49 [.48, .58]	-.01 [-.05, .17]	.50 [.41, .61]	10-fold	100
	.50 [.17, .75]	.47 [.25, 67]	.50 [.27, .58]	0 [-.45, .17]	.49 [.48, .58]	-.01 [-.05, .17]	.50 [.46, .55]	LOO	10

Note. Sensitivity is the true positive rate, recall or percent of correctly identified cases [TP/(TP + FN)]; specificity is the true negative rate or precent of correctly identified controls (TN/(TN+FP); [150,208]. Diag is the percentage of data points in the main diagonal of the confusion matrix

(TP+TN)/(TP+TN+FN+FP); Kappa is total correct percentage corrected for agreement by chance; Rand is Rand index measuring the similarity between two data clustering; Crand is Rand index corrected for by chance adjusted for chance [209,210].

Table 4

A Summary of the Performance of SVM-Based Models Trained on Young Adult Participants

Model	Sensitivity	Specificity	Diag	Kappa	Rand	Crand	Validation diag	Cross-validation	Repetition times
RBF (transformed_ mean_center)	.59 [.17, .92]	.57 [.17, 1]	.51 [.21, .73]	.02 [-.57, .46]	.51 [.48, .65]	.01 [-.04, .30]	.52 [.37, .66]	10-fold	100
	.51 [.25, .67]	.57 [.25, .75]	.47 [.27, .61]	-.06 [-.46, .21]	.51 [.48, .59]	.01 [-.04, .18]	.50 [.35, .65]	LOO	10
Linear (transformed_ mean_center)	.59 [.17, .92]	.59 [.25, 1]	.52 [.18, .81]	.04 [-.64, .62]	.51 [.48, .70]	.03 [-.04, .39]	.53 [.40, .72]	10-fold	100
	.61 [.42, 1]	.53 [.42, .67]	.50 [.38, .71]	0 [-.23, .43]	.50 [.48, .58]	0 [-.04, .15]	.54 [.46, .65]	LOO	10
RBF (transformed_ ordinal)	.66 [.25, .92]	.62 [.33, .92]	.56 [.31, .81]	.13 [-.38, .62]	.51 [.48, .68]	.02 [-.04, .35]	.58 [.43, .72]	10-fold	100
	.66	.60	.55	.10	.51	.02	.56	LOO	10

	[.42, .92]	[.25, .83]	[.29, .65]	[-.43, .31]	[.48, .58]	[-.04, .15]	[.50, .66]		
Linear (transformed_ ordinal)	.67 [.33, 1.17]	.59 [.17, .83]	.55 [.23, .73]	.10 [-.54. .46]	.51 [.48, .63]	.01 [-.04, .26]	.57 [.38, .68]	10-fold	100
	.65 [.25, 1]	.66 [.33, 1]	.57 [.32, .85]	.15 [-.36, .69]	.51 [.48, .73]	.02 [-.04, .46]	.59 [.44, .76]	LOO	10
RBF (non-transformed)	.53 [.17, .83]	.54 [.08, .92]	.47 [.27, .69]	-.06 [-.46, .38]	.50 [.48, .59]	0 [-.04, .18]	.50 [.44, .60]	10-fold	100
	.56 [.17, .75]	.58 [.42, .83]	.51 [.32, .65]	.01 [-.36, .31]	.50 [.48, .54]	.01 [-.04, .10]	.50 [.46, .56]	LOO	10
Linear (non-transformed)	.53 [.17, 1]	.52 [.17, 1]	.46 [.25, .65]	-.08 [-.50. .31]	.50 [.48, .62]	.01 [-.04, .22]	.49 [.38, .60]	10-fold	100
	.59 [.33, .83]	.52 [.25, .83]	.48 [.36, .64]	-.04 [-.29, .29]	.49 [.48, .53]	-.01 [-.03, .05]	.48 [.41, .59]	LOO	10

Note. Sensitivity is the true positive rate, recall or percent of correctly identified cases [TP/(TP + FN)]; specificity is the true negative rate or precent of correctly identified controls (TN/(TN+FP); [150,208]. Diag is the percentage of data points in the main diagonal of the confusion matrix

(TP+TN)/(TP+TN+FN+FP); Kappa is total correct percentage corrected for agreement by chance; Rand is Rand index measuring the similarity between two data clustering; Crand is Rand index corrected for by chance adjusted for chance [209,210].

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