基于Optuna-Stacking可解释机器学习模型揭示执行功能在精神分裂症辅助诊断与预后中的价值

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- Schizophrenia, a psychiatric disorder, is characterized by significant **pathological complexity** and **heterogeneity**(Owen et al., 2016, *Lancet*).

- Despite extensive research, its **etiology** remains elusive. Current **therapeutic strategies** frequently yield suboptimal results, contributing to a **substantial socio-economic burden worldwide**(Huang et al., 2019, *The Lancet Psychiatry*; Marder & Cannon, 2019, *New England Journal of Medicine*) .

- In-depth exploration of the **psychopathology** of schizophrenia, particularly the elements that trigger and maintain the mental disorder, could provide us with a **theoretical framework and tools** to unravel its **complexity**.

- Such investigation may lead to insights into its **causes**, how it **progresses**, and potential new ways to **treat** it(Borsboom et al., 2013, *Annu. Rev. Clin. Psychol*; Wright, et al., 2013, *Journal of abnormal psychology*).

- Executive functions (EFs), a set of cognitive processes that are necessary for the cognitive control of behavior, are **widely considered key** to understanding the complex mechanisms behind schizophrenia(Friedman & Miyake, 2017, *Cortex*).

- They are **closely linked to the psychopathology** of schizophrenia(Barch, 2005, *Annu. Rev. Clin. Psychol*; Kerns et al., 2008, *Biological Psychiatry*).

- However, EFs are not a singular entity **but a collection of diverse subcomponents**.Understanding the relationship between these diverse subcomponents and the psychopathology of schizophrenia **poses a significant challenge**, contributing to our current knowledge gap(Friedman & Miyake, 2017, *Cortex*).

- Given this backdrop, further research is imperative. Specifically, there is a pressing need to explore **whether these subcomponents could serve as robust metrics** for the diagnosis and prognosis of schizophrenia.

This study seeks to address **two** scientific questions through two sets of machine learning **classification models** .

- In aiding **diagnosis**, how do the unity and diversity of subcomponents of executive function contribute to the identification of patients with schizophrenia?

- In **prognosis**, can the subcomponents of EFs predict long-term treatment effects in patients with schizophrenia?

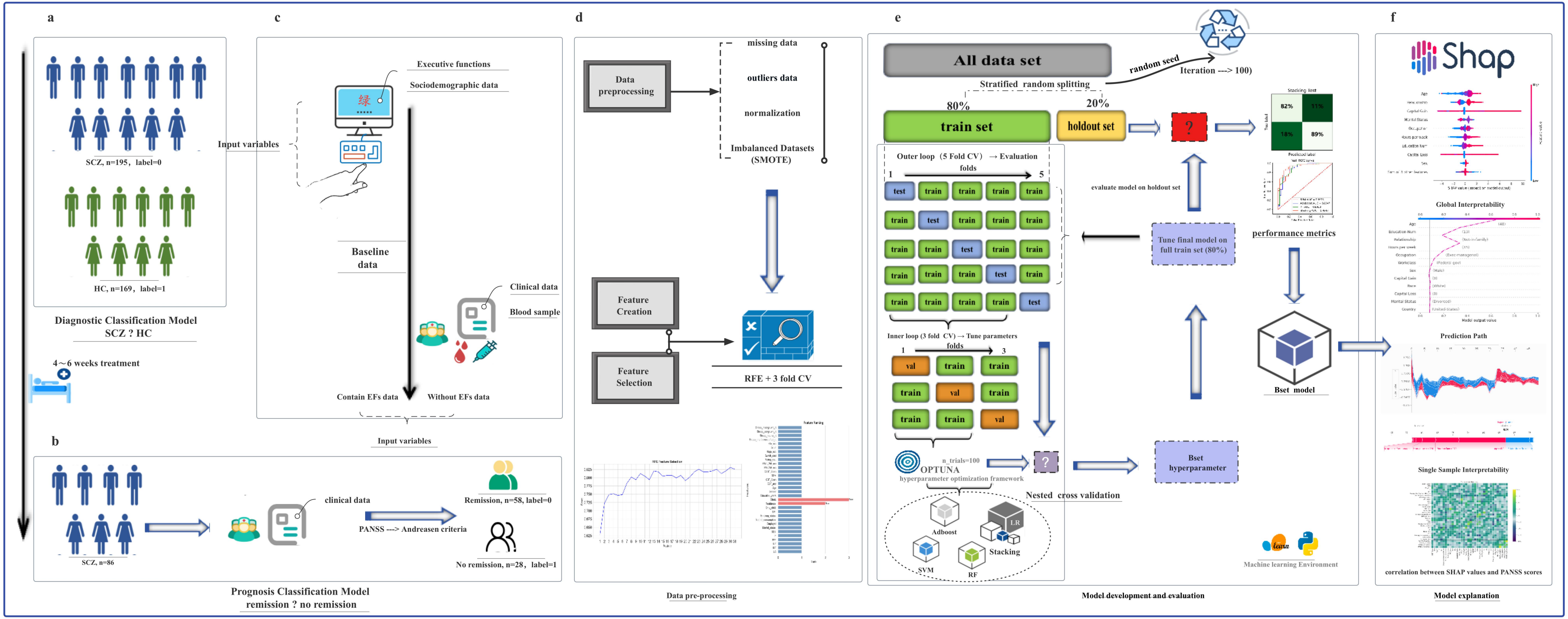

Fig.1 | Workflow for data collection to fully automated, individualized, and interpretable classification and prognosis models

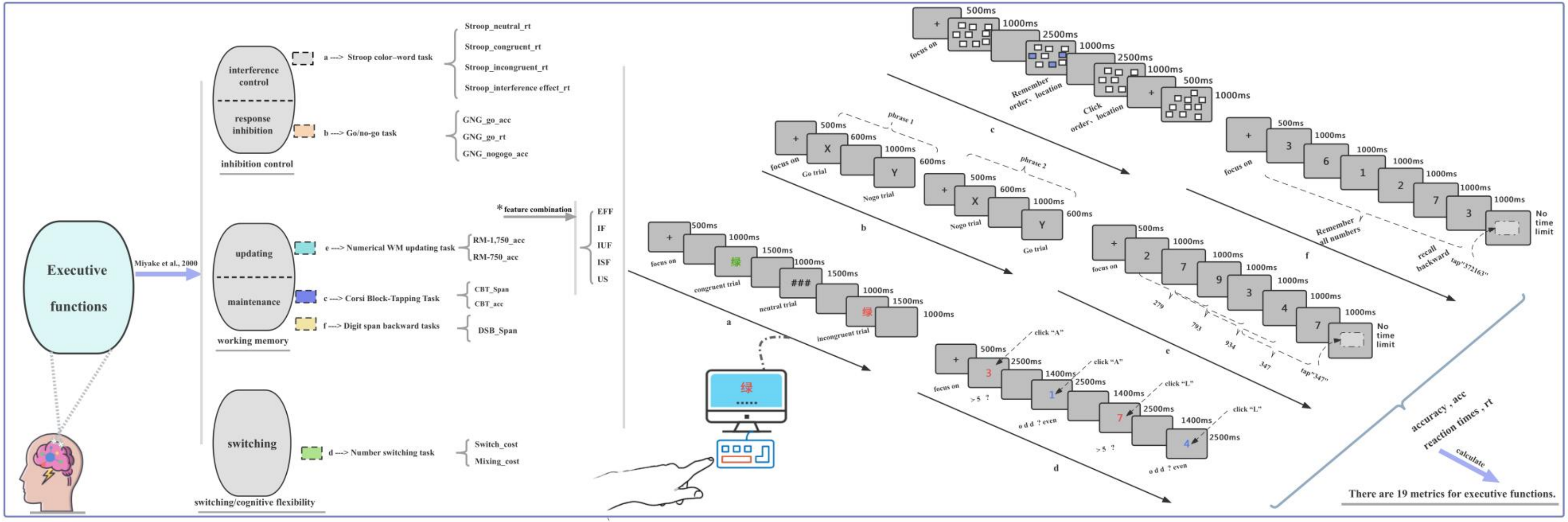

Fig.2 | Subcomponents of the execution function: partitioning method, behavioral measurement paradigms, and evaluation metrics

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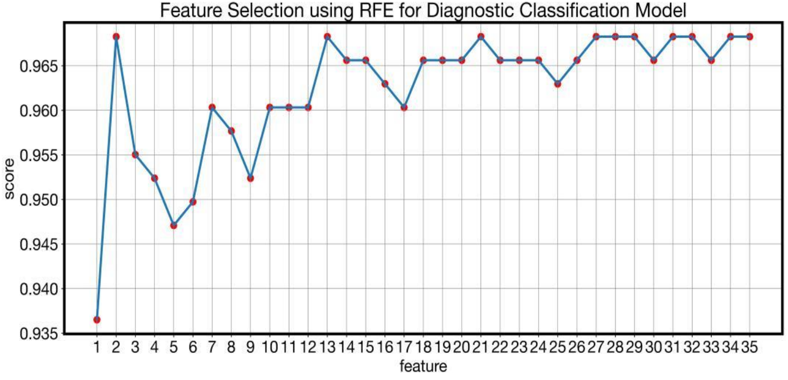

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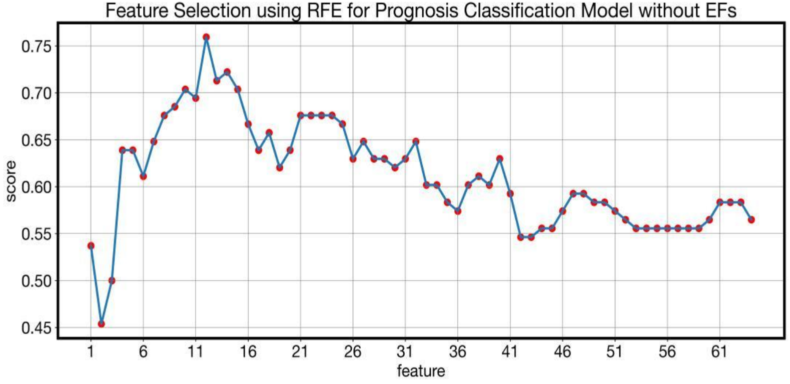

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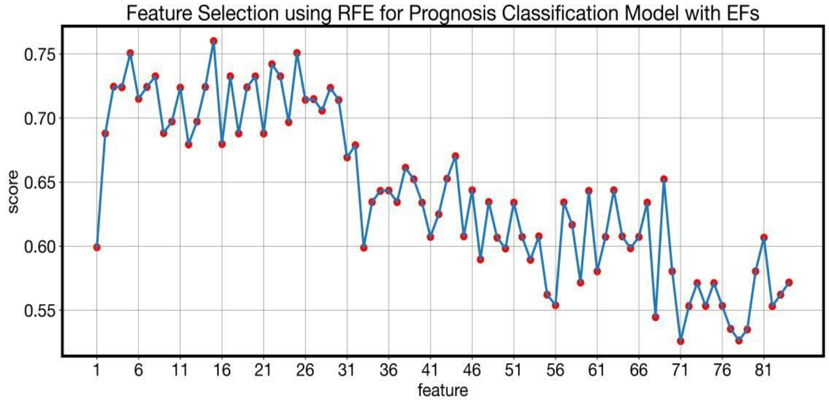
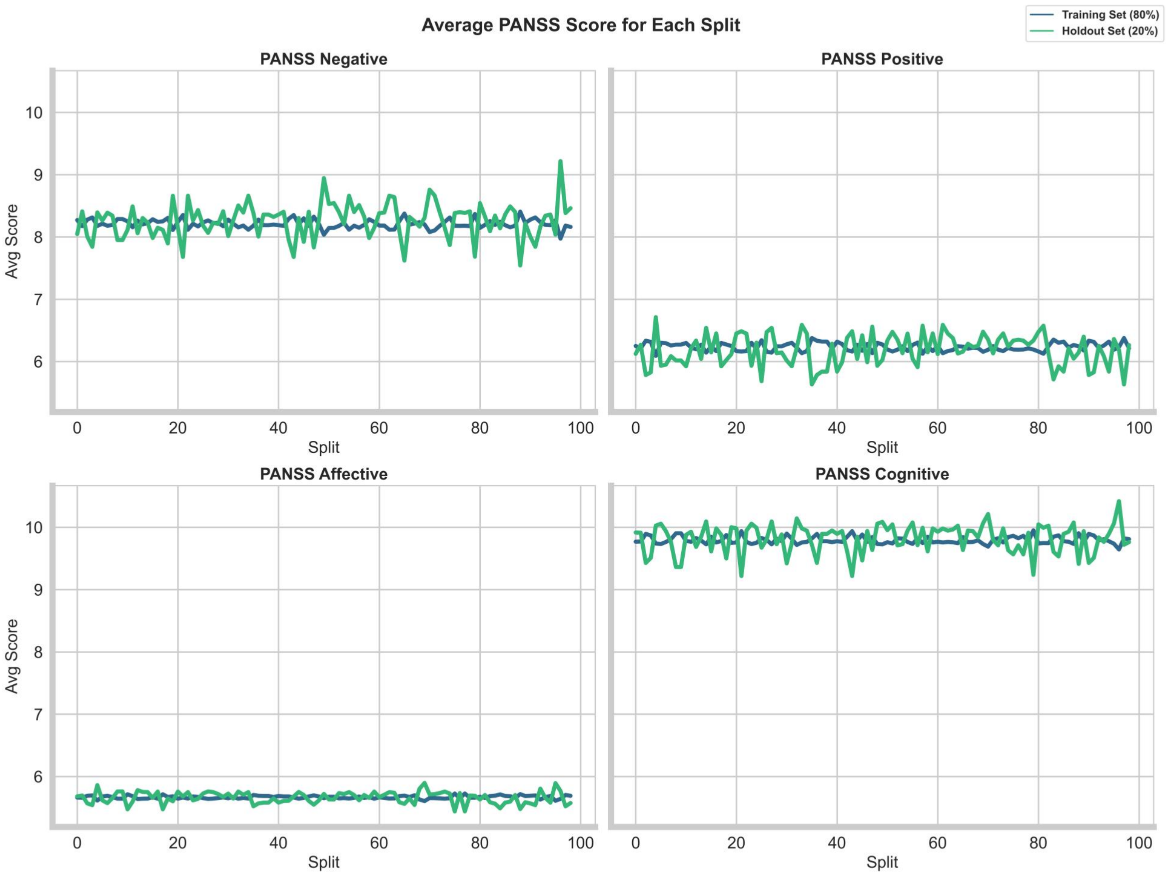


Supplementary Fig.1 | Feature selection results



Supplementary Fig.3 | Distribution of PANSS scores in patients in the training set and holdout set.

Table 2 | Results of machine learning classification models on holdout set (*M*±*SD*)

	Specificity	Sensitivity	Balanced Accurary	AUC
Diagnostic Classification Model				
SVM	0.832 ± 0.065	0.835 ± 0.179	0.834 ± 0.081	0.893 ± 0.131
RF	0.811 ± 0.064	0.882 ± 0.052	0.846 ± 0.036	0.919 ± 0.029
Adaboost	0.848 ± 0.073	0.835 ± 0.053	0.841 ± 0.038	0.912 ± 0.032
Stacking	**0.856 ± 0.060**	**0.888 ± 0.045**	**0.872 ± 0.033**	**0.941 ± 0.022**
Prognosis Classification Model with EFs				
SVM	0.715 ± 0.159	0.684 ± 0.159	0.654 ± 0.138	0.723 ± 0.155
RF	0.709 ± 0.152	0.745 ± 0.125	0.719 ± 0.096	0.785 ± 0.087
Adaboost	0.529 ± 0.158	0.695 ± 0.143	0.612 ± 0.104	0.627 ± 0.098
Stacking	**0.763 ± 0.126**	**0.765 ± 0.118**	**0.752 ± 0.084**	**0.818 ± 0.068**
Prognosis Classification Model without EFs				
SVM	0.725 ± 0.159	0.696 ± 0.171	0.688 ± 0.116	0.765 ± 0.135
RF	0.764 ± 0.115	**0.780 ± 0.122**	0.764 ± 0.087	0.844 ± 0.073
Adaboost	0.668 ± 0.150	0.712 ± 0.119	0.689 ± 0.082	0.725 ± 0.082
Stacking	**0.795 ± 0.121**	0.769 ± 0.128	**0.784 ± 0.077**	**0.864 ± 0.065**

SVM, Support Vector Machine; AdaBoost, Adaptive Boosting; RF, Random Forest; Stacking, Stacked Generalization; Bold numbers in the tableindicate the best performance for that metric.

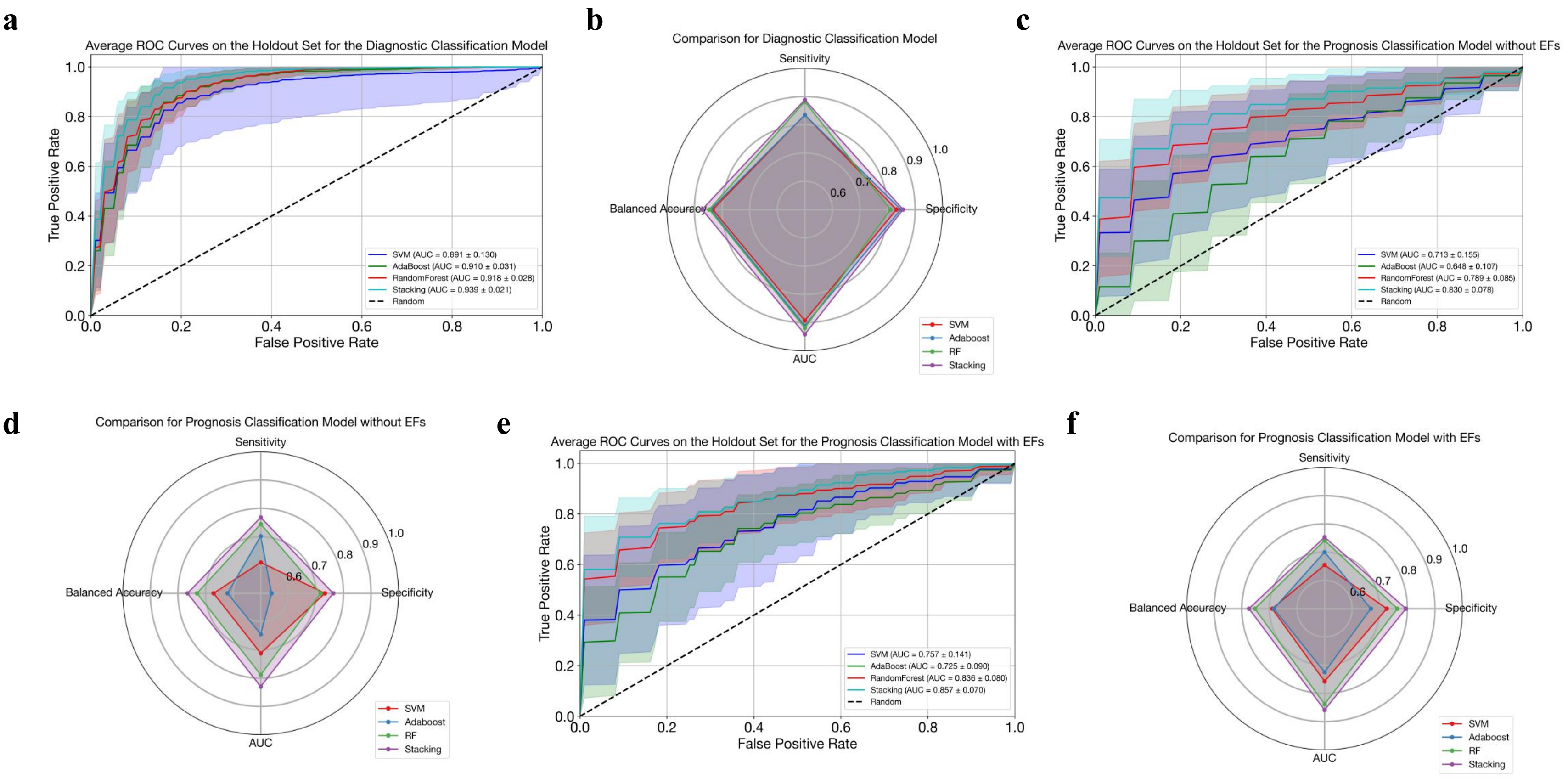


Fig.3 | Diagnostic and prognosis classification models with machine learning metrics

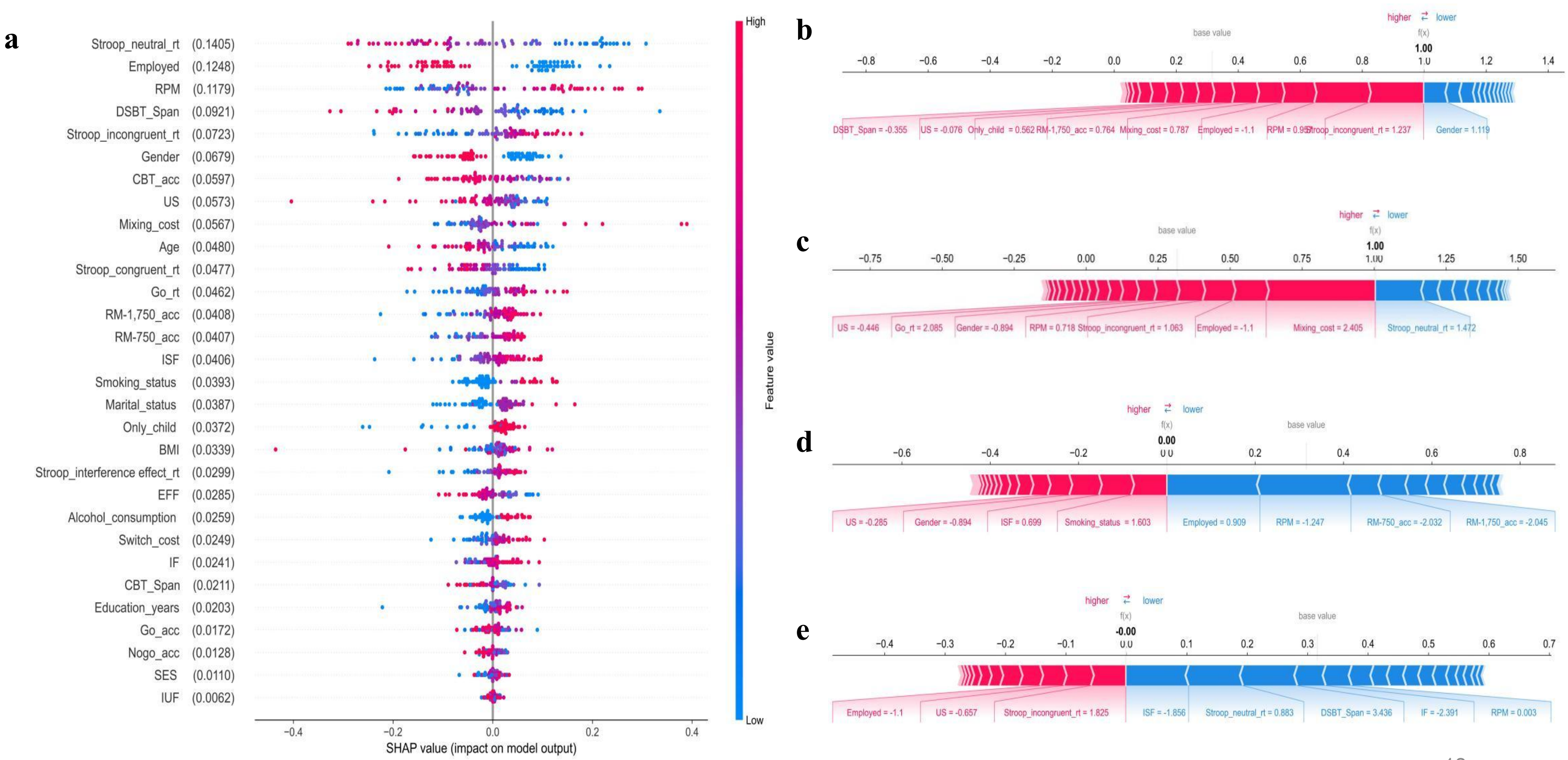


Fig.4 | Global and single-sample SHAP explanations for diagnostic classification models

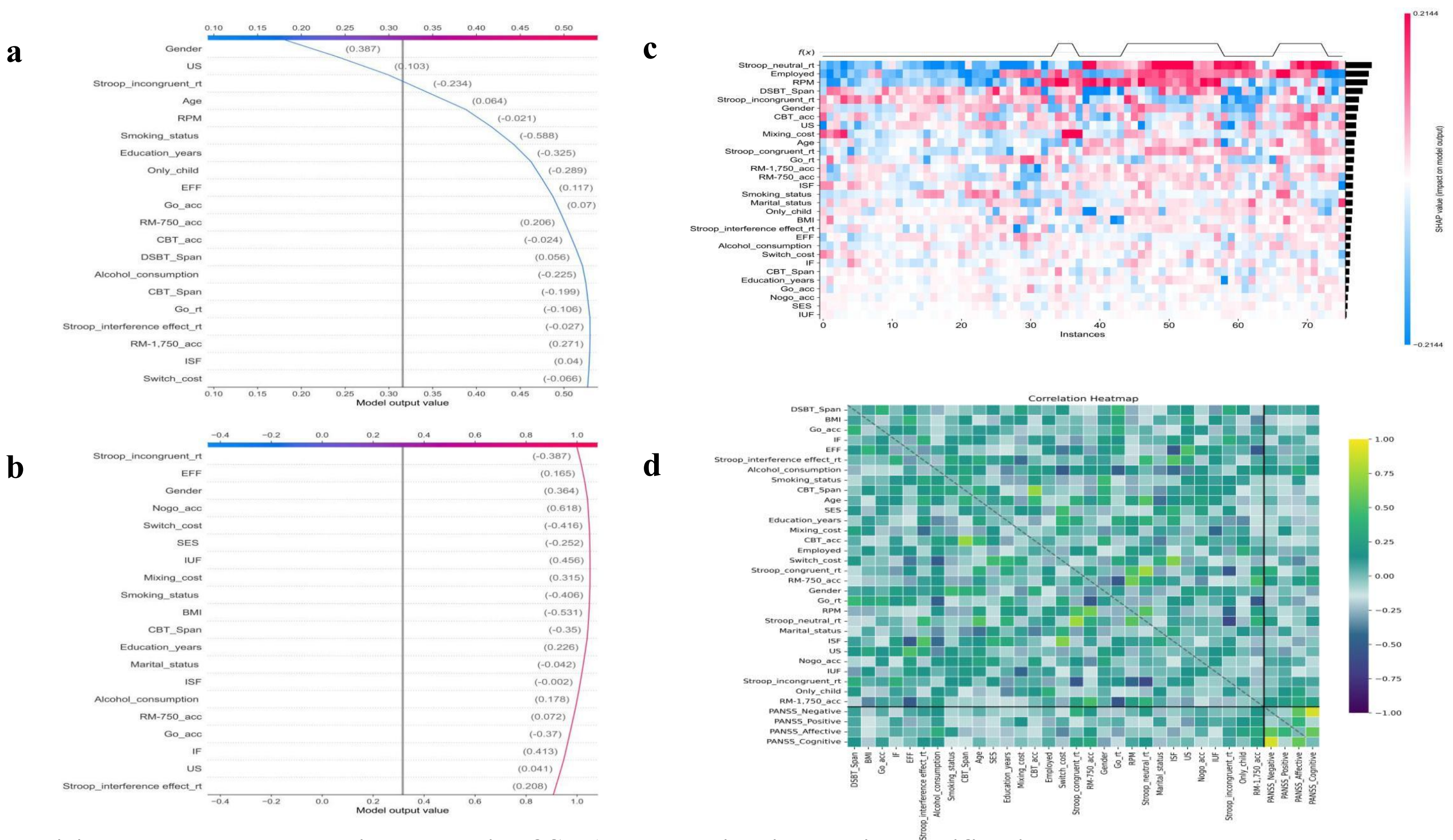


Fig.5 | Decision paths and correlation analysis of SHAP values in diagnostic classification models

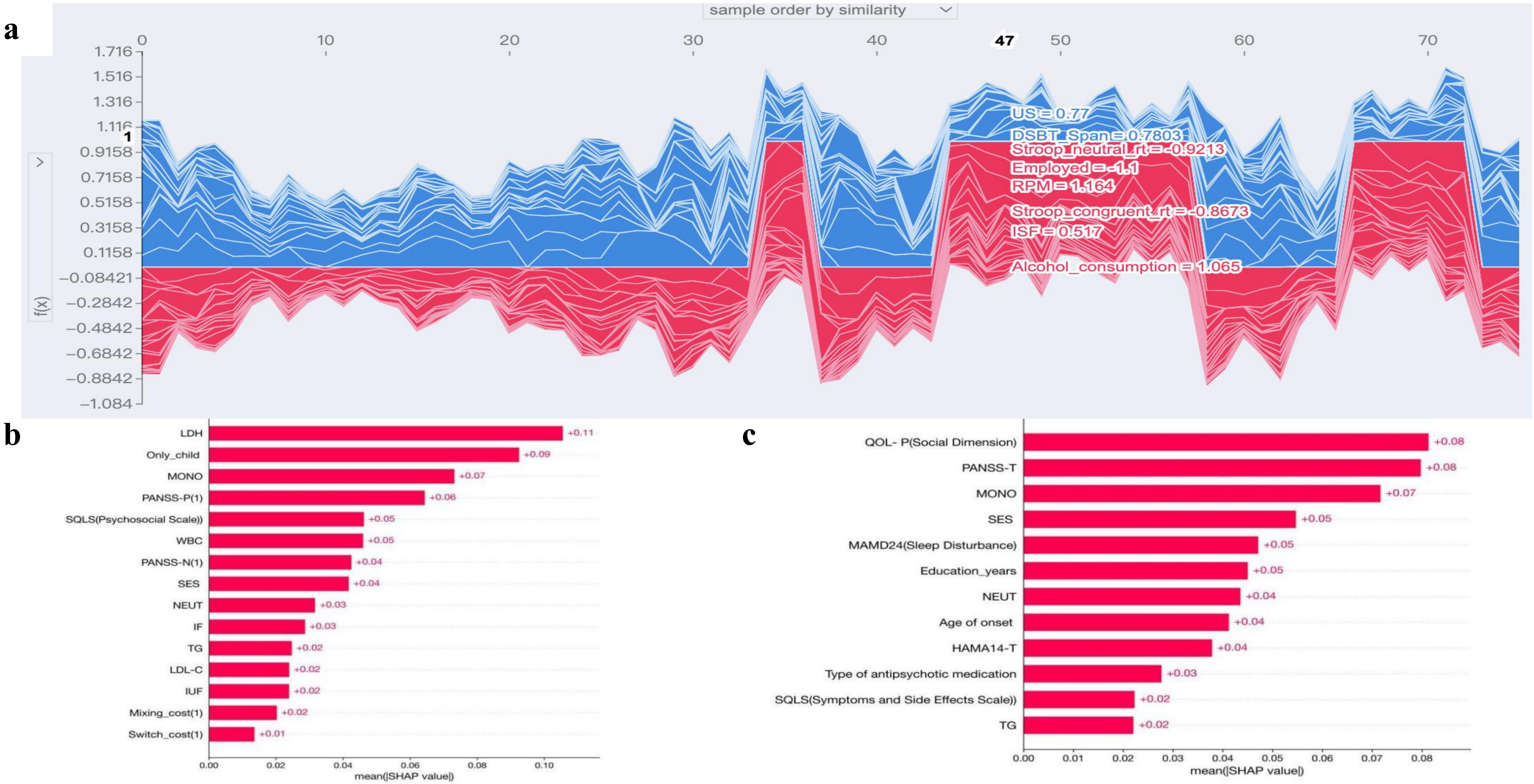


Fig.6 | Single-sample SHAP explanation combinations for diagnostic classification models and SHAP feature importance for prognosis classification models

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Compared to previous related classification diagnosis and prognosis studies,
our model has certain advantages.

- Our results showed that a Stacking model, which integrates multiple base learners including Support Vector Machines (SVM), AdaBoost, and Random Forest (RF), performed well (**Balanced accuracy = .866 ± .033; AUC = .938 ± .020**).

- Furthermore, our prognostic model, which includes baseline behavioral data of executive functions, clinical scales, demographic information, medical history, routine blood tests, and biochemical indicators, showed superiority in predicting the remission outcomes after **4-6 weeks** of treatment (**Balanced accuracy = .784 ± .077; AUC = .864 ± .065**).

2 ➥

- It is generally believed that features which yield higher accuracy likely represent the core aspects of the target, suggesting **a close tie with pathophysiology**(Chen et al., 2023, *Biological Psychiatry*).

- Our SHAP analysis revealed the importance of the Stroop task, which measures conflict inhibition, and the Go/Nogo task, which measures response inhibition, within the model.

- In essence, the diagnostic classification model constructed in this study harbors potential as a clinical decision support tool, assisting psychiatrists in diagnosis and treatment decisions.

Machine Learning Model → Clinical decision support tool

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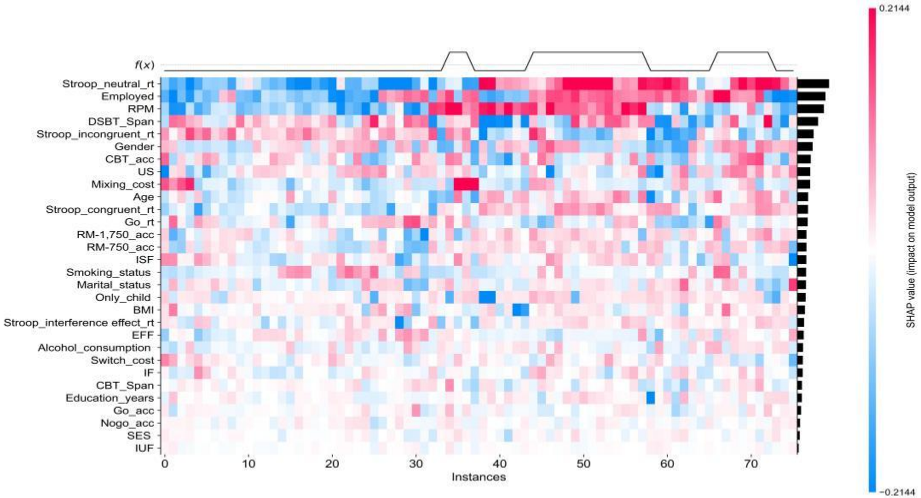

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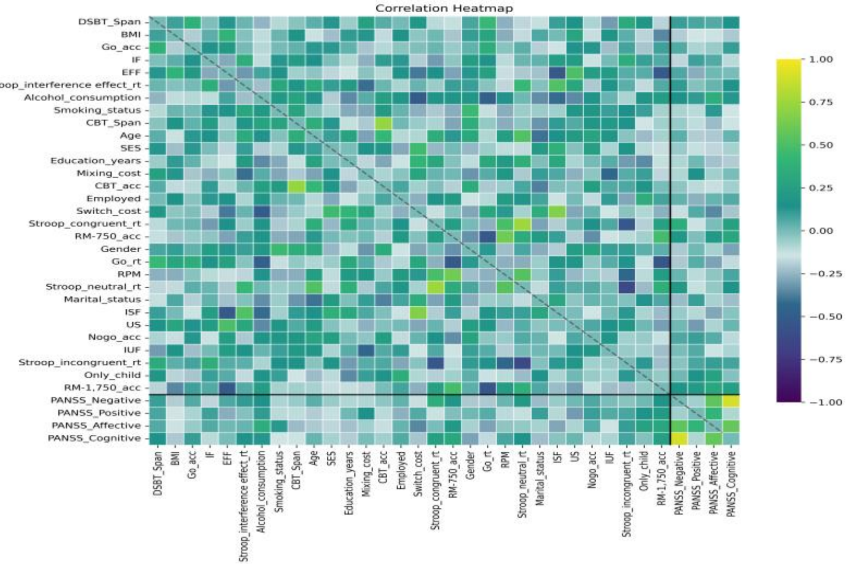

Fig.5 | Decision paths and correlation analysis of SHAP values in diagnostic classification models

Conlusions

- This study is the first to recognize the potential value of executive function subcomponents in **assisting the diagnosis of schizophrenia patients and assessing their treatment outcomes**, leveraging an interpretable machine learning classification model. This provides a novel perspective for understanding the **relationship between executive function and psychopathology**.

- While there is a prevailing interest in the brain mechanisms of executive function subcomponents and in classification models based on **brain imaging** data, our study suggests that cognitive behavioral tests can strike **a balance between the objectivity of data features and the ease of their acquisition**.

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恳请各位老师批评与指正

谢谢！