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Modulatory neurotransmitter genotypes shape dynamic functional connectome reconfigurations

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Abstract

Dynamic reconfigurations of the functional connectome across different connectivity states are highly heritable, predictive of cognitive abilities, and linked to mental health. Despite their established heritability, the specific polymorphisms that shape connectome dynamics are largely unknown. Given the widespread regulatory impact of modulatory neurotransmitters on functional connectivity, we comprehensively investigated a large set of single nucleotide polymorphisms (SNPs) of their receptors, metabolic enzymes, and transporters in 674 healthy adult subjects (347 females) from the Human Connectome Project. Pre-registered modulatory neurotransmitter SNPs and dynamic connectome features entered a Stability Selection procedure with resampling. We found that specific subsets of these SNPs explain individual differences in temporal phenotypes of fMRI-derived connectome dynamics for which we previously established heritability. Specifically, noradrenergic polymorphisms explained Fractional Occupancy, i.e., the proportion of time spent in each connectome state, and cholinergic polymorphisms explained Transition Probability, i.e., the probability to transition between state pairs, respectively. This work identifies specific genetic effects on connectome dynamics via the regulatory impact of modulatory neurotransmitter systems. Our observations highlight the potential of dynamic connectome features as endophenotypes for neurotransmitter-focused precision psychiatry.

Significance Statement

Understanding how genetic variations affect brain activity and connectivity can unlock new insights into cognitive abilities and mental health. This study reveals that specific genetic variations influence how long the brain stays in different connectivity states and how it

transitions between these states. These genetic variations were found in two modulatory neurotransmitter systems: acetylcholine and noradrenaline. These findings suggest that brain connectivity patterns influenced by genetics could serve as markers for personalized psychiatric treatment, pushing the boundaries of precision psychiatry.

1. Introduction

The time-varying characteristics of the brain's functional connectivity architecture (the connectome) are specific to the individual, highly heritable, and predictive of individual cognitive abilities[1–3]. Such dynamic characteristics consist of temporal features which depict the connectome's sequence of state (spatial connectivity patterns), i.e., the trajectory of the connectome through the space of possible states. These dynamic connectome features are associated with cognitive functioning and implicated in several psychiatric and neurological disorders[4–6]. Importantly, particular temporal features of connectome dynamics, such as the proportion of the total recording time spent in each connectome state (Fractional Occupancy) and the probability to transition between specific pairs of connectome states (Transition Probability), have been linked to behavioral performance[2,3,7] and found to be heritable[2,3]. Specifically, our previous work has established substantial genetic effects (h^2 ~ 40%) and strong behavioral relevance of Fractional Occupancy and Transition Probability[2]. This work further highlighted that such heritability is specific to the *temporal* features and does not encompass the *spatial* connectivity pattern and topology (specifically modularity) of the connectome states. Despite such strong support for genetic effects on the temporal characteristics of functional connectome dynamics, it is unknown which specific genes carry this effect. The goal of the current study is to identify genetic variants associated with these dynamic connectome phenotypes for which heritability has been established.

Recent theoretical advances and empirical evidence suggest that ascending neuromodulatory inputs play a pivotal role in driving such dynamic fluctuations in connectome states and cognitive functioning. This role may be due to the widespread volume transmission and long-lasting regulatory impact of modulatory neurotransmitters[8–11]. Unlike wiring transmissions, which involves rapid point-to-point signaling, neuromodulators such as acetylcholine and monoamines are commonly released non-synaptically, and instead diffusing through the extracellular space. Such diffusion allows a large number of cells to detect these neuromodulators through extrasynaptic receptors. Indeed, pharmacological studies have shown that the release of all core modulatory neurotransmitters – i.e. acetylcholine (ACh)[12], noradrenaline (NAd)[13], dopamine (DA)[14], and serotonin (5HT)[12,15–17]– can drastically alter large-scale connectome reconfigurations across various behavioral states. Further, spatial distributions of neurotransmitter receptors are aligned with the structural and intrinsic connectivity networks[16,18,19], facilitating the flow of information and supporting cognitive processes[20].

Single nucleotide polymorphisms (SNPs), the most common form of genetic variation [21], have been extensively studied for their role in shaping individual differences in brain structure and function [22]. As specific and measurable genetic variants, SNPs enable fine-grained analyses of genetic contributions to brain function. SNPs can modify a gene's function by either altering its expression or by modifying the composition of its product, i.e., the protein, through changes of amino acids or splice variants, to name the most common means. Therefore, we propose that SNPs in the genes, encoding receptors, metabolic enzymes, and transporters of the modulatory neurotransmitter

systems, are likely contributors to the heritability of dynamic connectome state transitions and associated cognitive functions.

If empirically confirmed, such genetic impact of neurotransmitter systems on connectome dynamics and cognition would have implications for understanding mental health. Connectome dynamics are implicated in numerous psychiatric and neurological conditions[23] and explain individual differences in certain cognitive abilities across different diagnostic categories[24]. Regarding Fractional Occupancy and Transition Probability in particular, associations have been observed with major depressive disorder[4], schizophrenia[5], and subjective cognitive decline[6]. Moreover, the patho-etiology of most psychiatric disorders involves abnormalities of neurotransmitter-related proteins, such as receptors dysfunction and neurotransmitter imbalance[25]. Consequently, most pharmacological interventions for psychiatric disorders target modulatory neurotransmitter systems[26,27]. Not surprisingly, specific SNPs in these systems may contribute to individual differences in symptoms and treatment response[28,29]. Therefore, it is likely that modulatory neurotransmitter systems impact mental health and cognitive functioning through dynamic reconfigurations of the functional connectome, and that polymorphisms in the former shape the latter.

Despite such strong translational implications for putative genetic effects on functional connectome dynamics, previous genetics neuroimaging studies have not investigated the dynamic connectome. These studies have primarily focused on the association between genetic polymorphisms and structural connectivity[22,30], *static* (time-averaged) functional connectivity[22,31–33], and more broadly cortical volume[30] and network activations[20,34–36]. Further, most of the previous work has separately examined the impact of each *individual* genetic polymorphism of interest on brain imaging phenotypes. However, in a complex biological system, phenotypic expression typically results from the joint contribution of multiple genetic factors. Therefore, our study aimed to fill a critical knowledge gap by demonstrating how genetic polymorphisms of the modulatory neurotransmitter systems jointly shape the heritable phenotypes of the functional connectome dynamics, i.e., Fractional Occupancy and Transition Probability[2].

To this end, we examined a comprehensive list of SNPs from genes encoding ionotropic and metabotropic receptors, metabolic enzymes, and transporters for each modulatory neurotransmitter system (ACh, NAd, DA, 5HT). The quality control and inclusion/exclusion criteria of the SNPs as well as definition of connectome and cognitive phenotypes followed our pre-registered project (https://doi.org/10.17605/OSF.IO/VF2ZW). For each neurotransmitter system, we employed a five-fold cross validation approach with a stable feature selection algorithm (Stability Selection)[37–39] to explain each connectome phenotype. This approach aimed to identify the *joint* contribution of all SNPs in each neurotransmitter system to the connectome dynamics phenotypes. Further, in light of the established relationship between the above-described connectome dynamics phenotypes and cognitive abilities[2,3,7], we examined whether the same set of SNPs that explained connectome dynamics could concomitantly explain variability in cognitive abilities.

2. Materials and Methods

Figure 1 is a schematic representation of the overall approach and analysis subsections. SNP selection and phenotype definition followed our pre-registered project. Note that statistical analyses deviated from the pre-registered project because we identified a testing approach more pertinent to the goal of the present study[40], which we were not aware of at the time of pre-registration (cf. its successful application in comparable genotype-phenotype association studies[41,42]).

2.1. Subjects

We used genetics, resting-state fMRI, and behavioral data from the Washington University-University of Minnesota (WU-Minn) consortium's Human Connectome Project (HCP) S1200 release[43]. Participants were recruited, and informed consent was acquired by the WU-Minn HCP consortium according to procedures approved by the Washington University IRB[44].

The genotyping data for 1,141 subjects was made available through the dbGAP repository. Briefly, the DNA samples were collected from either whole blood or saliva sample and genotyped using the Illumina Multi-Ethnic Global Array (MEGA) SNP-array. This array included chip-specific content from PsychChip and ImmunoChip and provided comprehensive coverage of European, East Asian, and South Asian populations. To maintain ethnic homogeneity, only subjects with European genetic ancestry were included in the study using the genetic ancestry predicted with the SNPweights software package[45,46] (*Figure 1-1*). Consequently, 674 healthy adult subjects (aged 22–36 years, 347 females) with four complete resting-state fMRI scans (4800 total timepoints) were included. Further details on the HCP data collection protocol[43,47], cognitive measures[48], and inclusion and exclusion criteria [43,47] can be found elsewhere.

2.2. Genotype Imputation

Genotype imputation for the SNPs of interest (see below) was performed using minimac4 method and the HRC reference panel (version r1.1, which consists predominantly of European ancestry) through the Michigan Imputation Server (accessed on 29 January 2022)[49]. Prior to the imputation process, we conducted quality control of the HCP data using the toolbox provided by Will Rayner (http://www.well.ox.ac.uk/~wrayner/tools/; accessed on January 29, 2022). This step was taken to ensure the data was properly organized to be imputed with the HRC reference panel. The input data was prepared following the guidelines provided by the Michigan Imputation Server. The genotype imputation was done for each chromosome after several quality control and phasing steps by the server.

2.3. SNPs selection and quality control

We targeted a specific set of SNPs in the genes that encode receptors, metabolic enzymes, ion channels, and transporters of modulatory neurotransmitters (i.e., ACh, NAd, DA, and 5HT) in the human brain following our pre-registered selection procedures. Specifically, we selected 60 genes related to these neurotransmitter

systems from the Neurotransmitter Study (*Figure 1-2*) conducted by the Allen Institute for Brain Science. These genes were characterized by in situ hybridization (ISH) in the adult human brain. The SNPs associated with these genes were identified using the Variant Effect Predictor (VEP; https://useast.ensembl.org/info/docs/tools/vep/) tool. In particular, we identified SNPs with the upstream and downstream distance of 5000 bp from the gene as a buffer (which is a default setting of VEP and a common choice in the field) meeting specific criteria, including having a Minor Allele Frequency (MAF) greater than 0.05, as well as being of either intron, synonymous, or missense variant types. These criteria were chosen to ensure that the selected SNPs represent common genetic variations and are pertinent to gene expression regulation and protein function. Further, we used GTEx Portal (https://gtexportal.org/; accessed on 02 November 2021) to quantify each SNP's expression quantitative trait loci (eQTL) in cortical tissue, then selected SNPs with eQTL p-value less than 0.05. This additional step allowed us to hone in on SNPs with substantial influence on gene expression in the cortex.

After identifying the SNPs to be included in the study, quality control measures were taken on the imputed HCP data using PLINK v2.0[50]. SNPs with a MAF < 5%, a Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$), missing call rates (> 10%) across individuals were removed. Additionally, individuals with missing call rates (> 20%) across the genotypes were excluded. Linkage disequilibrium (LD) analysis was conducted, and SNPs were greedily pruned until no pairs with $r^2 > .2$ within a 500kb sliding window with a step size of 50 markers (Note that this value was updated from the originally pre-registered 50kb window upon a reviewer request at the revision stage of the manuscript). The list of SNPs selected after the process is reported in *Figure 1-3*. Population structure and kinship were modeled as described in the statistical analyses below.

2.4. Neuroimaging data preprocessing and parcellation

With the goal of investigating specifically those connectome phenotypes that we previously established as being heritable[2], all neuroimaging procedures correspond to those that were performed in our prior work and resulted in the pre-registered phenotype selection. The procedures are included here for completeness. Imaging data were acquired on a customized Siemens 3T Skyra at Washington University in St. Louis using a multi-band sequence. Each subject had four 15-minute resting-state fMRI runs. We used the data that were minimally preprocessed by the HCP consortium[44] with the pipeline of Smith et al.[47,51] using tools from FSL[52] and Freesurfer[53] and artifact removal using ICA+FIX[54,55]. Inter-subject registration of the cerebral cortex was carried out using areal feature-based alignment and the Multimodal Surface Matching algorithm ('MSMAll')[56,57]. The HCP team had previously parcellated the neuroimaging data using Independent Component Analysis (ICA) in FSL with model orders of 25, 50, 100, 200, and 300 and provided averaged BOLD time-series data for regions of these group-ICA-based parcellations. For the present study and our previous work[2], the 300-model order ICA was chosen and its time-series data was used without global signal regression. However, Automated Anatomical Labeling (AAL) atlas-based masks and visual inspection identified that 161 out of 300 independent components were either from cerebellar or brainstem. Therefore, the focus of our investigation was on the 139 independent components from the cortical and subcortical cerebrum, which represent

the canonical intrinsic connectivity networks. The reconfigurations of these canonical networks have been described as key contributors to the behavioral impact of connectome dynamics[58–60]. Further details on cerebral parcellation can be found in our previous work[2].

2.5. Hidden Markov modeling and temporal features of the connectome dynamics

The following briefly describes the procedures performed in our prior twin heritability study that provided the foundation for the current investigation[2]. The hidden Markov model (HMM) assumes that time series data can be represented by a finite sequence of hidden states. Each HMM-inferred connectome state, along with its corresponding time series, represents a unique connectivity pattern that temporally re-occurs over time. Using the HMM-MAR (multivariate autoregressive) toolbox[61], we applied the HMM to the minimally preprocessed, region-wise BOLD time-series and obtained four discrete connectome states (*K* of 4; *Figure 1-4*). Specifically, the number of states (*K*) was chosen following our previous work[2] which identified heritability of the temporal connectome dynamics phenotypes using $K = 4$ and replicated the findings using $K = 6$. Such *K*s were selected based on prior HMM studies that have directly compared several Ks and identified *K*s between 3 and 7 as optimal[61,62]. Further details on the HMM and reasonings for the selection of *K* can be found in our previous work[2].

HMM-derived estimates describe the temporal aspects of connectome dynamics by characterizing the sequence of connectome states or the connectome's trajectory through state space. Specifically, we calculated Fractional Occupancy (the cumulative total time spent in a given state; $1 \times K$) and Transition Probability (the probability matrix of transitioning between all possible pairs of discrete states; $K \times K$) for each subject. While Transition Probability and Fractional Occupancy are not fully independent measures, they do provide non-overlapping information about connectome dynamics. For example, a state with particularly high Fractional Occupancy is likely to have high values as initial state and target state in the Transition Probability matrix. Despite such dependence, however, two hypothetical subjects with highly comparable Fractional Occupancy values across the *k* states may still have substantially different Transition Probability matrices. Our previous work demonstrated strong genetic effects on these temporal characteristics of functional connectome reconfigurations[2].

Our phenotypes of interest (i.e., Fractional Occupancies and Transition Probabilities) span multiple brain states and are inherently multi-dimensional. While recent methods extend genetic association analyses to multivariate phenotypes, these approaches involve several assumptions and may increase type I error rates[63]. As our prior work[2] demonstrates the heritability of the multivariate phenotypes after dimensionality reduction, we believe that important phenotypic information is retained after such reduction.

To reduce the dimensionality of Fractional Occupancy and Transition Probabilities as in our prior work[2], we calculated the distance of individuals from an origin point. Specifically, we generated surrogate data to derive the origin point from which the Euclidean distance of each multivariate phenotype was estimated for each subject.

Surrogate datasets were simulated using the *simhmmmar* function from the HMM-MAR toolbox, which preserves the static covariance structure of the original data while disrupting the precise temporal ordering of states. An HMM inference with $K = 4$ states was applied to each of 50 surrogate datasets, and Fractional Occupancy and Transition Probability were recomputed. The Fractional Occupancy (respectively Transition Probability) values averaged across the surrogate datasets were used to determine the origin point. Further details on obtaining the origin point from the null models can be in our previous work[2].

2.6. Cognitive performance

The following briefly describes the factorization that was performed in our prior heritability study and resulted in preregistered cognitive phenotypes of interest[2]. Specifically, we included 14 cognitive measures provided by the HCP, which are summary scores from cognitive tasks or questionnaires under the cognition domain (see *Figure 1-5* for more information on each variable). The measures were normalized to have zero mean and unit variance. A factor analysis was then conducted to cluster the cognitive measures into four Cognitive Factors[2]. The Cognitive Factors were interpreted as follows: factor 1: “Language”; factor 2: “Impulsivity/self-regulation”; factor 3: “Cognitive control”; and factor 4: “Memory”. Further details on the factor analysis can be found in our previous work[2].

2.7. Statistical analysis

We evaluated the *joint* effect of the neuromodulatory SNPs on the temporal phenotypes of the connectome dynamics, i.e., Fractional Occupancy and Transition Probability. Specifically, separately for each neurotransmitter system, we aimed to build a model incorporating the optimal combination of SNPs and covariates that best explains each temporal connectome dynamics phenotype. Note that SNP genotypes were dummy coded as 0/1/2 to represent subjects with 0, 1, or 2 copies of the minor allele, which is according to the standard additive model applied in genetic association studies.

To avoid overfitting, we employed a 5-fold cross-validation approach (Figure 1C)[64]. This approach involves splitting the full data into equally sized five folds and using $4/5^{th}$ of the data as train set and the remaining $1/5^{th}$ of the data as test set, then rotating which $1/5^{th}$ is used for testing. When combined, the five test sets form the original full data. It’s important to note that participants from the same family were assigned to the same fold.

In each train set, we used the Stability Selection procedure[37,38] with elastic net regression as the selection algorithm to identify a subset of predictors that best explains each of the connectome phenotypes. Specifically, for each connectome phenotype, SNPs of a modulatory neurotransmitter system and covariates (i.e., age, sex, frame-wise displacement (FD) calculated across the entire scan duration for head motion, and 10 principal components that account for European-ancestry population structure) entered a Stability Selection procedure[37,38] through the R package *stabs* (https://cran.r-project.org/web/packages/stabs/index.html). We opted for Stability Selection procedure as our selection algorithm because it offers greater stability compared to other regularization methods (e.g., stepwise regression or elastic net without Stability

Selection)[39]. The method also generates more parsimonious models by reducing the unmodelled variability to the estimates and, thus, mitigating the risk of type 1 errors. As such, Stability Selection has been widely used in the fields dealing with high-dimensional data, such as gene regulatory networks[65], genome-wide association studies[66], and graphical modeling[67,68].

Specifically, Stability Selection implemented a complementary pairs subsampling approach[38,39], which involved dividing a given train set into 50 random pairs of subsamples (where each subsample comprised half of the data) and conducting variable selection on each subsample. Variables selected in a predetermined proportion of the subsamples were retained. Typically, the proportion threshold is preselected in the recommended range of 0.6 to 0.9[37]. We chose a threshold of 0.75 that balances rigorous selection with the risk of false negatives[69].

Then, we fitted two models to the values of a connectome phenotype in the test set (i.e., the left-out fold): (i) the "full model" comprising a subset of covariates and SNPs selected by Stability Selection on the train set, along with random genetic effects in the form of a kinship matrix, and (ii) the "base model," which included only the selected covariates and the kinship matrix (excluding SNPs). Note that the base model was identical to the full model, except for the absence of SNPs. The kinship matrix, representing family structure, was obtained using the *lmekin* function in the R package *coxme* (https://cran.r-project.org/web/packages/coxme/index.html). Importantly, we did not *predict* the test set using the parameter weights of these two models derived from the training set. Instead, we fitted the two models (i.e., full and base models) directly to the test set and obtained the residuals, respectively. This approach was necessary because accounting for the kinship in the linear mixed-effects models, a critical step to adjust for the random genetics effect in the data with families, does not allow using the pre-defined parameter weights obtained from the training set and, obviously the kinship matrix differs between the training and testing samples. This process was repeated 5 times, with each fold serving as the test set once.

Consequently, each subject had two residuals: one from the full model and the other from the base model. The absolute values of these residuals were then concatenated across subjects, i.e. across the five test sets[70,71]. To assess whether the full model fits the data significantly better than the base model, the two sets of residuals entered an *F* test. In the regression context, the numerator degrees of freedom (df1) are related to the number of parameters being tested, which is the difference in the number of parameters between the full and the base models. The denominator degrees of freedom (df2) are related to the number of observations minus the number of parameters in the full model. In order to compute the F statistics and P values with the most conservative approach, we set the df1 to be largest by taking the maximum number of parameters from the full models and the minimum number of parameters from the base models across the five folds. All statistical analyses were performed in R.

Subsequently, in a second analysis, the above-described neurotransmitter models – specifically built for each of the connectome dynamics phenotypes– underwent further testing to evaluate their explanatory capacity for cognitive abilities. Specifically, each of

the neurotransmitter models that outperformed the base model was tested for a new set of phenotypes: the Cognitive Factors, i.e., Language, Impulsivity, Cognitive Control, and Memory. The “cognitive full model” was fitted to the test set, which includes the same subset of SNPs and covariates selected above for each fold and the kinship matrix as predictors and each of the Cognitive Factors as a dependent variable. Simultaneously, the “cognitive base model” was fitted to the same test set, consisting only of the above-selected covariates and the kinship matrix. The significance of each cognitive model against their respective cognitive base model was tested using the same approach (*Table 2-1*).

3.Results

Consequent to the selection and quality control process of the genotype data (Figure 1A), a total of 155 SNPs were included in the present study (*Figure 1-3*): 25 SNPs from 14 ACh genes, 9 SNPs from 4 NAd genes, 38 SNPs from 5 DA genes, and 83 SNPs from 17 5HT genes. Two heritable connectome phenotypes and four associated cognitive phenotypes were adopted from our prior twin study[2].

3.1. Effects of select SNPs on temporal connectome phenotypes

Stability Selection (Figure 1C) identified a subset of SNPs for each neurotransmitter system that best explained the connectome states’ Fractional Occupancy or Transition Probability, respectively. The SNPs and covariates included for each model by Stability Selection are listed in *Table 1-1*. We found two neurotransmitter models that significantly outperformed the covariates-only base model ($P^{\dagger} < .05$, where $P^{\dagger}$ is the Bonferroni-corrected P value for eight models; Table 1). Specifically, Fractional Occupancy was explained by the noradrenergic model ($F(2, 671) = 6.56$, $P^{\dagger} = .012$), and Transition Probability was explained by the cholinergic model ($F(3, 670) = 12.25$, $P^{\dagger} = 6.61e\text{-}07$). The significant models included SNPs related to two NAd alpha-1 receptors, both G protein-coupled receptors (*ADRA1A* and *ADRA1D* genes), an ACh metabolic enzyme (*BCHE* gene), and ACh nicotinic ion channels (*CHRNB1, CHRNB4, and CHRNA2* genes). To provide an intuition, Figure 2 illustrates how one polymorphism contributing to a significant association model is linked to each connectome dynamics phenotype. Note that while the illustration highlights a single SNP for demonstration purposes, the significance of the models emerged from the synergistic impact of the respective SNPs in combination.

For completeness, we also tested each of the 155 SNPs individually (along with the covariates) in separate linear regression models. This analysis represents our originally pre-registered association approach prior to identifying and adopting an established and stable approach[37,38] to unveil the impact of multiple SNPs. When tested individually in this manner, none of the SNPs survived a highly conservative correction method (Bonferroni-corrected $P < .05/155$), strengthening the notion that the SNPs are associated collectively, rather than individually, with the investigated connectome dynamics phenotypes.

Table 1. Neurotransmitter models explaining temporal connectome dynamics phenotypes

NT models	Predictors selected from five train sets			Full model vs. base model		
	Predictors (# selected)	Genes	Protein family	*F* value	*P* value	$P^{\dagger}$ value
Fractional Occupancy						
NAd	rs35105284 (5x)	*ADRA1D*	NAd alpha 1 receptor	*F*(2, 671) = 6.56	.0015	.012
	rs1048101 (2x)	*ADRA1A*	NAd alpha 1 receptor			
	rs60593443 (1x)	*ADRA1A*	NAd alpha 1 receptor			
	Sex (4x)					
	Age (1x)					
Transition Probability						
ACh	rs1803274 (3x)	*BCHE*	ACh enzyme	*F*(3, 670) = 12.25	8.26e-08	6.61e-07
	rs2302761 (1x)	*CHRNB1*	ACh nicotinic ion channel			
	rs2565061 (1x)	*CHRNA2*	ACh nicotinic ion channel			
	rs3743072 (1x)	*CHRNB4*	ACh nicotinic ion channel			
	rs1948874 (1x)	*SLC44A5*	Choline transporter			
	n_ps3 (5x)					
	Sex (1x)					
	Age (1x)					

During the five-fold cross validation, modulatory neurotransmitter SNPs and covariates entered the Stability Selection algorithm on the train set (4/5th of the data) five times. The table shows how many times each SNP and each covariate were selected by Stability Selection across the five folds. NT: Neurotransmitter, ACh: acetylcholinergic, NAd: noradrenergic, DA: dopaminergic, # selected; number of each predictor selected across the 5 folds, $P^{\dagger}$: P values Bonferroni-corrected for 8 tests. *$P^{\dagger} < .05$. Note that ACh model of Fractional Occupancy and 5HT model of Transition Probability outperformed the covariates-only base model. See Extended Data Table 1-1 for the complete list of predictors selected from stability selection across five training sets for each temporal connectome dynamics phenotype and neurotransmitter system and Table 1-2 for gene expression levels of the select genes in the seven canonical intrinsic connectivity networks.

3.2. Effects of select SNPs on cognition

In accord with our pre-registered hypotheses, we tested whether the above-described models containing a set of SNPs that explain connectome dynamics phenotypes can also explain cognitive abilities. Specifically, the NAd model of Fractional Occupancy and the ACh model of Transition Probability were fitted to each of the four Cognitive Factors. In other words, the multi-SNP models initially built for connectome phenotypes were re-fitted to cognitive phenotypes. We found two models explaining cognitive abilities compared to their respective base model ($P^{\dagger} < .05$, where $P^{\dagger}$ is the Bonferroni-corrected P value for 8 models in Table 2; see full results in *Table 2-1*). Specifically, the NAd SNPs originally identified in each fold to explain Fractional Occupancy explained Language and Memory factors.

Table 2. Neurotransmitter models explaining Cognitive Factors

Re-fitted models	Mean Residuals concatenated across five test sets		Cognitive full model vs. Cognitive base model		
Cognitive Phenotype	Cognitive base model	Cognitive full model	*F* value	*P* value	$P^{\dagger}$ value
NAd model explaining Fractional Occupancy					
Language	<.001	<.001	F(2, 671) = 66.52	4.24e-27	3.54e-26
Memory	0.026	0.017	F(2, 671) = 363.62	1.05e-107	8.42e-106

Modulatory neurotransmitter SNPs and covariates selected using Stability Selection algorithm on the train set (4/5th of the data) in each fold for the temporal connectome dynamics phenotypes were re-fitted to each of the Cognitive Factors. NAd: noradrenergic, DA: dopaminergic, $P^{\dagger}$: P values Bonferroni-corrected for 8 tests (two significant models in Table 1 and four Cognitive Factors). *$P^{\dagger} < .05$. See Extended Data Table 2-1 for complete results of the neurotransmitter models explaining of Cognitive Factors.

Discussion

The complexity of brain function and cognitive abilities arise from brain dynamics, including the functional connectome that changes dynamically over time. Such time-varying connectome dynamics, which are highly heritable, predictive of cognitive abilities[2,3], and linked to mental health[4,6], may be modulated by the modulatory neurotransmitter systems[10,72,73]. However, the specific genetic polymorphisms that shape connectome dynamics have been largely unknown. The current study departs from previous genetics neuroimaging investigations of *static* functional connectome measures[31–34] and reveals that genetic profiles of modulatory neurotransmitter systems impact *dynamic* connectome phenotypes, specifically Fractional Occupancy and Transition Probabilities. Our findings provide evidence for genetic effects on connectome dynamics via the regulatory impact of modulatory neurotransmitter systems.

Interestingly, the genetic impact on dynamic connectome phenotypes was observed in the NAd and ACh systems, the two modulatory neurotransmitter systems that have been hypothesized to drive functional connectome dynamics through their cooperative and competitive impact on neural gain (output as a function of input)[8]. Notably, we observed

a double dissociation in how these neurotransmitter systems contribute to the connectome phenotypes, with the NAd system (specifically alpha 1 receptor genes) explaining Fractional Occupancy and the ACh system (most notably nicotinic ion channel and enzyme genes) explaining Transition Probability. This observation indicates that distinct neural mechanisms support Transition Probability and Fractional Occupancy, which contain non-overlapping information about connectome dynamics (although they are not fully independent measures; cf. **Methods 2.5**). However, understanding of the mechanisms behind the differential effects of modulatory neurotransmitters on connectome phenotypes will require dedicated studies in the future.

The observed contribution of neurotransmitter systems to the heritability of connectome dynamics aligns with the role of these systems in driving widely distributed but spatially organized neuromodulation. Neuromodulatory neurotransmitter receptors and transporters are spatially distributed according to canonical intrinsic connectivity networks and functional gradients that are hallmarks of the connectome's architecture, thereby effectively mediating the connectome-wide propagation of synaptic communication and population activity[8,18,74]. *Table 1-2* showcases this distributed gene expression across the intrinsic neurocognitive networks[75] for each of the genes identified in Table 1 using the microarray data of the Allen Institute for Brain Science. In dedicated studies, this spatial organization may provide mechanistic insights into *how* genetic variation in neurotransmitter systems may modulate connectome states' Fractional Occupancy and Transition Probabilities. As an example in prior literature, combining spatial mapping of a serotonergic receptor with modelling and pharmacological intervention (serotonergic agonist psilocybin), the causal chain from serotonergic neuromodulation to connectome state's Fractional Occupancy and Transition Probabilities has been outlined[16,17]. Building on our current findings, such models can be extended to include the subjects' receptor/enzyme/transporter genotypes to mechanistically understand inter-individual variability in connectome-level effects of neuromodulation.

The identified genetic impact of modulatory neurotransmitter systems on connectome dynamics may help understand the patho-etiology of various neurological and psychiatric conditions and predicting treatment response. For instance, the *ADRA1D* gene was consistently identified in the noradrenergic model of Fractional Occupancy (Table 1 and *Table 1-1*). *ADRA1D*, along with *ADRA1A* which contained all other identified NAd-related SNPs, encode NAd alpha 1 receptors whose activation contributes to cortical arousal (including enhanced excitability[76,77]). Alpha 1 receptors thus serve as a pharmacological target (for receptors-specific antagonists) in post-traumatic stress disorder characterized by hyper-arousal[77]. The observed association between *ADRA1* receptors and connectome dynamics may help explain the previously established link between physiological arousal fluctuations and functional connectome dynamics[78]. Further, the *BCHE* gene was repeatedly selected in the cholinergic model of Transition Probability (Table 1 and *Table 1-1*). The *BCHE* gene encodes the butyrylcholinesterase enzyme that inactivates acetylcholine and consequently its modulatory impact on processing of environmental stimuli[79]. *BCHE* is thought to

contribute to accelerated deactivation of acetylcholine in the aging brain[80,81] and is implicated in mild cognitive impairment[82] and Alzheimer's disease[80,81] While *BCHE* expression in astrocytes is widely distributed across the brain, the expression in neurons is particularly high in limbic areas[83,84] (as confirmed in *Table 1-2*), regions that play a critical role in Alzheimer's dementia. Butyrylcholinesterase is considered a potential therapeutic target for Alzheimer's disease, which is characterized by a cholinergic deficit[85]. It is interesting to note that the specific rs1803274 variant of *BCHE* gene found in our study has been strongly associated with the serum level of the butyrylcholinesterase[86]. As connectome features have the potential to inform individualized medicine[87], the genes we identified may help to refine treatment efforts that embrace inter-individual differences in connectome dynamics.

In addition, we found that the noradrenergic model, which explained Fractional Occupancy, also explains cognitive factors characterized by performance in the domains of language and memory (Table 2). It is important to note that the specific emergence of Language and Memory factors in this association closely aligns with our previous heritability work in the same dataset[2]. Specifically, the prior work showed that connectome phenotypes that were identified as heritable (and hence entered the current study) exhibit the strongest cognitive association with the same Language factor, followed by the Memory factor. Interestingly, a prior study[88] that investigated heritability of *behavioral* measures, likewise in the HCP dataset, demonstrated the highest heritability in two cognitive factors with task loadings similar to those of our Language and Memory factors. Collectively, these findings not only suggest that both subject-specific trajectories across connectome states and cognitive abilities are under genetic effects, but also that the noradrenergic polymorphisms may drive the relationships between connectome phenotypes and cognition[9–11,13,89], specifically between Fractional Occupancy and Language/Memory.

Our study is subject to several limitations which must be considered when interpreting our findings. Firstly, while we identified polymorphisms associated with connectome dynamics, in some cases it is yet to be revealed whether they change the functional capability of the respective proteins. Specifically, beyond missense protein-coding SNP the identified models contained introns and synonymous SNPs (e.g. rs35105284; *ADRA1D* gene). Such inclusion of synonymous SNPs and introns is in line with the observation that complex traits are primarily associated with noncoding variants that likely impact gene regulation[90]. Furthermore, our work should be interpreted at the level of identified genes rather than individual SNPs, as we have focused on investigating variants which have significant influence on gene expression (eQTL $p < .05$), which is their most likely mechanism of action. Finally, it is important to note that the genes identified in our study and their encoded products (such as receptors or metabolic enzymes) function as components of intricate system-level networks[91] influenced by various biological and environmental factors, making mechanistic interpretation of our results challenging. For example, different receptors have distinct binding affinities, downstream signaling pathways, and cellular responses to varying levels of neuromodulatory neurotransmitters. Additionally, neural activity can also impact gene expression and neurotransmitter function[92,93]. Thus, the associations between specific

genes and connectome phenotypes identified in our study should be interpreted cautiously and further investigated in the future in terms of the underlying molecular and cellular mechanisms. The discoveries from our study motivate investigations into such potentially indirect (i.e. regulatory) impact of the identified SNPs on the respective proteins[94], and suggest that such impact translates into connectome states' Fractional Occupancy and Transition Probability phenotypes. Moreover, our study is based on a relatively small size of the European-ancestry population due to the difficulty in finding a consortium-level dataset with publicly available genotype and high-quality resting-state fMRI data of young adults, calling for future replication upon availability of such data. Further, because ethnic differences in the frequency or the effect size of a variant can affect the likelihood of its discovery and its contribution to phenotypes across populations, a study cannot include subjects from multiple ethnic groups. Future studies should replicate our approaches in other ethnic groups and compare the roles of potentially different neurotransmitter genetic profiles in modulating the connectome dynamics and cognition.

To conclude, our study reveals specific genes that modulate dynamic connectome reconfigurations. This work extends beyond prior studies that have primarily focused on static connectome measures. We demonstrate that multiple SNPs in each neurotransmitter system are critical in shaping the dynamic trajectory of the functional connectome in state space. Our study has the potential to inform the development of precision medicine strategies that leverage genetic information to tailor diagnostics and interventions for mental health disorders.

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Author Contributions: SJ and SS designed research; SJ performed research; SJ analyzed data; SJ and SS wrote the paper; and SS and AA contributed analytic expertise, theoretical guidance, and informed interpretation of the results.

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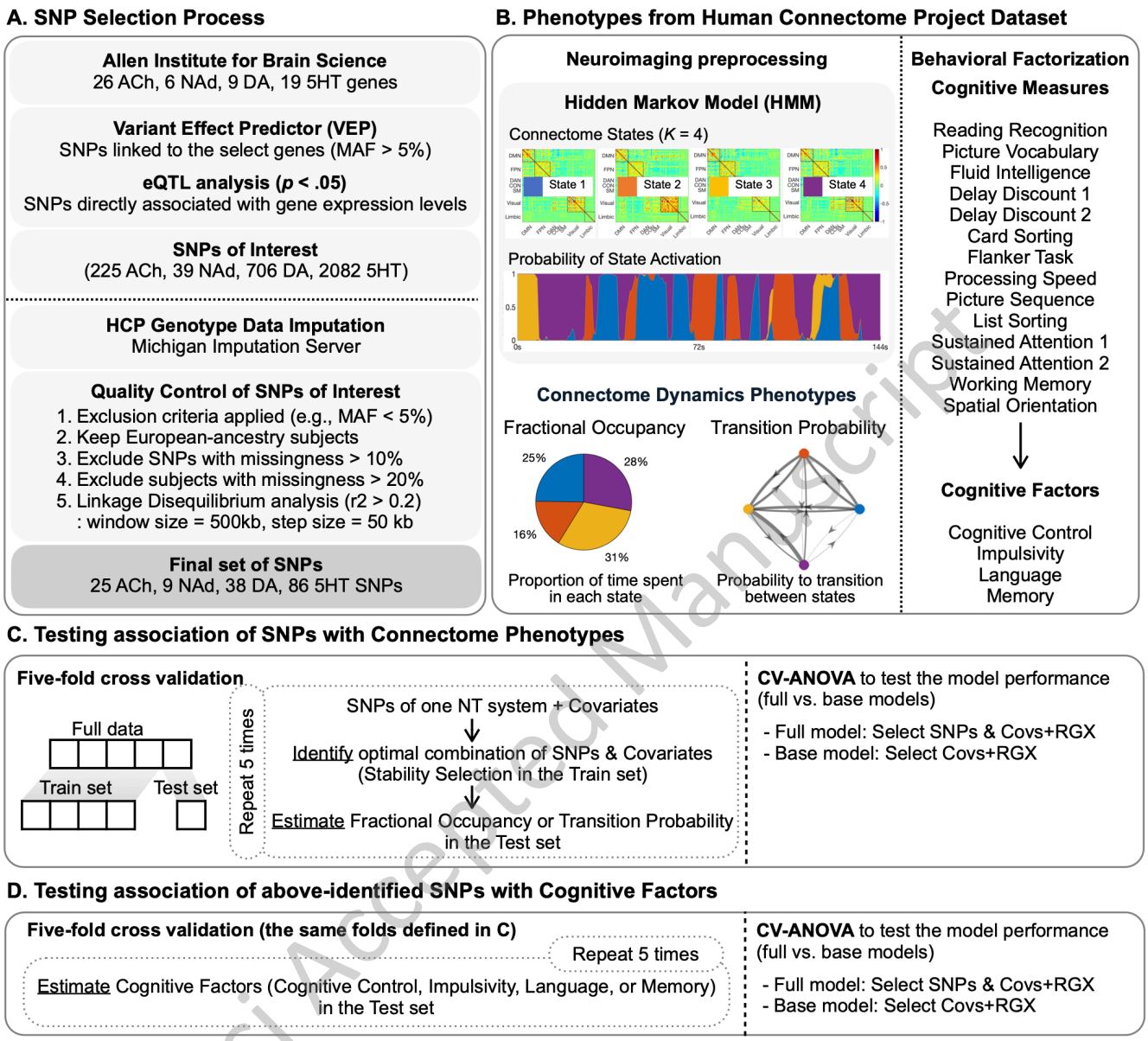
Figure Legends

Figure 1. An overview of the analysis pipeline. Panels A and B follow the steps outlined in our pre-registered project to determine genotypes and phenotypes entering the study. Specifically, the top section of Panel A describes the process of selecting the single nucleotide polymorphisms (SNPs), while the bottom section details the imputation and quality control steps carried out on the Human Connectome Project (HCP) genotype data. The left side of Panel B depicts the hidden Markov model (HMM) estimates of temporal phenotypes (i.e., Fractional Occupancy and Transition Probability) of functional connectome dynamics [2]. The right side of Panel B illustrates the factorization of the various cognitive measures obtained from the HCP dataset. Note that as a foundation for the current study, we have previously established the heritability of the connectome and cognitive phenotypes depicted in Panel B using a twin study approach in the same data[2]. In Panel C, we divided the data into five subsets for each connectome phenotype and neurotransmitter system. Within the training set (comprising 4/5th of the full data), we employed Stability Selection approach, which utilizes elastic net regularization and resampling techniques, to select a subset of SNPs and covariates (age, sex, head motion, and 10 principal components representing the European-ancestry population structure) that best explain each temporal phenotype. Subsequently, we used this subset in the "full model" (including the selected SNPs, covariates, and random genetic effects (RGX)) and the "base model" (including the same subset of covariates and RGX, but not SNPs) to be fitted to the test set. This process was repeated five times. For each connectome phenotype and neurotransmitter system, we combined the residuals from the full and base models across the five test sets and used a linear mixed-effects model to assess model performance (full vs. base). In Panel D, we re-fitted the full models that outperformed their respective base models in Panel C to be fitted to each of the Cognitive Factors in the same test sets. Subsequently, we combined the residuals of the “cognitive full” and “cognitive base” models across the five test sets and used a linear mixed-effects model to evaluate model performance. Refer to Extended Data Figure 1-1 for a visualization of the population stratification of all HCP subjects with genotype data, Figure 1-2 for the list of 60 selected genes from the Neurotransmitter Study of the Allen Institute for Brain Science, Figure 1-3 for the 155 SNPs included in the analysis after quality control, Figure 1-4 for a detailed visualization of the four HMM-derived states, and Figure 1-5 for information on the 14 cognitive measures used in the analysis.

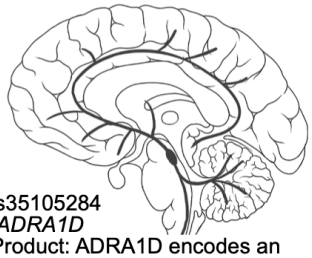
Figure 2. An illustration of genetic polymorphisms associated with temporal connectome dynamics phenotypes. To provide an intuition of the association, the figure uses the example of rs35105284, a SNP included in the significant noradrenergic (NAd) model of Fractional Occupancy. Averaged across the subjects of a given genotype, the pie charts depict the mean duration of time spent in each connectome state. For example, subjects with the homozygous genotype for major allele (T/T) of rs35105284 spend more time in state 4 and less time in state 3 compared to minor allele

carriers (T/C and C/C). Note that while this illustration highlights a single SNP for demonstration purposes, the significance of the models often emerged from the synergistic impact of several SNPs in combination.



Examples of the Genotypes affecting Temporal Phenotypes of the Connectome Dynamics

The Noradrenergic System



SNP: rs35105284
Gene: *ADRA1D*
Gene Product: ADRA1D encodes an transmembrane protein that functions as G protein-coupled receptors.