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Personalized Network Mapping Reveals State-Trait Dissociation of Frontoparietal Connectivity in Adolescent Depression: A Longitudinal Study

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Abstract

Prior research linking resting-state networks (RSNs) to adolescent depression has yielded inconsistent findings, partly because group-average templates poorly capture individual brains; a mismatch that may be especially consequential during adolescence, when RSNs grow increasingly heterogeneous across individuals. Using a personalized analysis pipeline in the longitudinal *Characterizing Adolescent Trajectories of Depression* cohort (38 depressed adolescents [28 female]; ages 14–18; 181 usable scans; avg. participation: 446.18 days), we derived individualized definitions of three canonical depression-related RSNs. Because longitudinal RSN connectivity may reflect both trait-like vulnerability and state-like symptom fluctuation, we used mixed-effects models to decompose connectivity profiles into both components. FPN connectivity showed a significant state-trait dissociation: chronically elevated connectivity predicted greater average symptom burden, while transient increases predicted momentary relief. These effects were undetectable using group-atlas estimates. We suggest FPN connectivity plays a dual, compensatory role in adolescent depression and demonstrate that personalized definitions can reveal clinically meaningful brain-symptom associations.

Introduction

From the beginning of puberty through the mid-twenties¹, adolescence represents a period of heightened risk for the onset of most psychiatric disorders, including Major Depressive Disorder (MDD). An estimated 13–20% of adolescents experience at least one depressive episode before age 18^{2,3}, and the burden is growing: incident cases among 15- to 19-year-olds rose nearly 30% between 1990 and 2021⁴, with depression projected to cost the global economy over \$12 trillion by 2050⁵. Relative to adult-onset depression, adolescent-onset depression follows a more severe and recurrent illness course, with unique neuroimaging signatures, greater functional impairment, higher rates of suicidality, and elevated risk for comorbidities in adulthood^{6–8}. This same developmental window is marked by profound, experience-dependent specialization of association cortices that may also confer heightened vulnerability to psychiatric illness, including depression⁹. Together, these findings underscore the need to better understand the neurobiological mechanisms that give rise to and sustain depressive illness during adolescence.

Resting-state fMRI (rsfMRI) is particularly well-suited for investigating the large-scale networks implicated in depression, as it captures spontaneous, intrinsic functional coupling between distributed brain regions without requiring a specific task. Unfortunately, rsfMRI studies of adolescent depression have produced inconsistent results, partially due to the field's past reliance on cross-sectional designs. Cross-sectional approaches capture a single snapshot of brain–symptom associations across individuals, conflating two fundamentally different sources of variance: stable, *trait*-level differences between people in their average neural functioning, and dynamic, *state*-level fluctuations within individuals over time. This distinction is both theoretically and clinically important in the context of MDD: a *trait*-level association would suggest that a chronic pattern of network functioning confers a dispositional risk, whereas a *state*-level association would suggest that an individual's momentary neural functioning tracks their current symptomatic state. Because cross-sectional designs cannot disentangle these two signal sources, conflating within- and between-person effects in a single analysis can produce misleading estimates of both¹⁰.

Dense sampling designs in which individuals are scanned repeatedly over a sufficient period of time permit investigators to decompose neural predictors into stable, person-level averages (between-person differences) and session-level deviations from those means (within-person fluctuations) in order to estimate *trait* versus *state* associations with depressive symptoms within the same statistical model¹¹. Despite this advantage, to our knowledge, only one prior rsfMRI study of adolescent-depressive symptoms has formally decomposed within- and between-person connectivity effects¹²; instead, most studies with more than one observation per-subject focus on trajectory-level or age-related effects rather than session-to-session covariation with symptoms¹³. Inconsistent findings on how brain connectivity relates to depressive symptoms¹⁴ may reflect the fact that studies have not distinguished stable, *trait*-level differences in functional network integrity from their dynamic, *state*-level fluctuations¹⁵.

Neuroimaging studies using rsfMRI have implicated several large-scale resting-state networks (RSNs) in the pathophysiology of adolescent depression. The default mode

network (DMN), associated with self-referential thought and rumination^{16,17}, the salience network (SN), which orients attention toward salient stimuli and modulates transitions between the DMN and task-positive networks^{18,19}, and the fronto-parietal network (FPN), which supports cognitive control^{20,21}, together have been implicated in self-regulatory (e.g., emotion regulation) and motivational deficits that characterize MDD²². Although recent studies have consistently implicated the DMN, SN, and FPN in adolescent depression, the exact directionality of these patterns has been inconsistent^{14,23,24}. Studies have variously reported increased, decreased, and unchanged functional connectivity within and between these networks in depressed adolescents relative to healthy peers, with modest effect sizes that often do not replicate across cohorts^{17,25}. A recent meta-analysis found no single network showing consistent directional effects across studies¹⁴. This heterogeneity likely reflects a combination of small sample sizes and methodological variability, including differences in clinical characterization, preprocessing pipelines, and, critically, how RSNs are defined and measured, both between and within individuals.

Nearly all rsfMRI studies of adolescent depression utilize group-average parcellation atlases (e.g., Yeo, Power, and Schaefer atlases^{26–28}) to spatially define RSNs, an approach that relies on two assumptions: that RSN topography is consistent across individuals, and that adolescent RSN organization resembles an adult topography. Both assumptions are particularly problematic in developmental clinical samples. First, RSN topography varies substantially across individuals, even in healthy adults, such that functional connectivity patterns are distinctive enough to reliably identify a person from a database^{29–31}; applying a shared atlas to individuals whose network boundaries deviate from the template conflates true network signal with nearby, functionally distinct regions³². Second, and most critically when analyzing developmental samples, adolescent RSN organization does not yet resemble the adult templates from which these atlases are derived: networks that comprise much of association cortex undergo protracted, spatially heterogeneous maturation well into the mid-twenties^{9,33,34}, producing RSN boundaries that are less well-defined and more variable across individuals than is typically observed in adults^{35–37}. Moreover, the RSNs that support the affective, cognitive, and self-regulatory functions disrupted in MDD are among the most variable across individuals of all large-scale networks^{9,31,38} and sit in close spatial proximity to one another, with adjacent, interdigitated regions whose boundaries differ from person to person³⁹. A group-average atlas is therefore particularly likely to misassign cortex between networks most relevant to depression, introducing a developmentally naive spatial mismatch that may interact with clinical variables such as depression severity^{40,41}. Systematically misidentifying which network is which in each person offers a plausible explanation for the mixed rsfMRI literature on adolescent depression. Contemporary research has sought to address the developmental gap, specifically, by creating pediatric and/or adolescent-centric atlases^{42,43}; nevertheless, the principle of between-person heterogeneity remains increasingly salient during adolescence.

The present study addresses these gaps by leveraging the Characterizing Adolescent Trajectories of Depression (CAT-D) study⁴⁴, in which adolescents with MDD

completed an average of 4.75 scans over approximately 14.5 months. We use independent component analysis (ICA) to derive individualized DMN, SN, and FPN definitions for each participant, validated against canonical RSN templates, and test whether this individualized approach reveals brain–symptom associations not captured by a standard atlas-based parcellation. The repeated-measures design of CAT-D allows us to statistically dissociate within-person (*state*) from between-person (*trait*) connectivity effects, testing whether connectivity in the DMN, SN, and FPN relate differentially to depressive symptoms. We hypothesize that (1) within-person and between-person connectivity will show dissociable associations with depression severity, reflecting distinct *state* and *trait* contributions, and (2) individualized network definitions will yield stronger brain–symptom associations than atlas-based definitions.

Results

Our analysis included 38 depressed adolescents from the CAT-D cohort (73.7% female), contributing a total of 181 resting-state fMRI sessions (mean $\pm$ SD = 4.76 ± 1.99 scans, range: 3–11 scans; inter-scan interval = 127.26 ± 64.48 days, range: 6–490 days; see details in **Supplemental Figure 1**). Participants were between ages 14–18 (16.16 ± 1.24 years) and were, on average, followed for over a year (446.18 ± 172.35 days, range: 129–851 days). At baseline, 60.5% ($n = 23$) of participants were taking antidepressant medication, and 5.3% ($n = 2$) were receiving inpatient care. The sample was predominantly White (76.3%, $n = 29$), with 7.9% ($n = 3$) identifying as Asian, 7.9% ($n = 3$) as biracial, and 5.3% ($n = 2$) as Black. Further details can be seen in **Table 1**.

1.1 Individualized networks show atlas-recognizable topography but substantial divergence across cumulative canonical boundaries

Before presenting brain–behavior associations, we characterized how well the sample’s individualized (ICA-derived) RSNs corresponded to canonical network definitions. For each participant ($N = 38$), the independent component (IC) with the greatest spatial correspondence to each network was identified by comparing its spatial (Dice) overlap with four independent reference atlases (see further details in **methods section 2.3.2**). Averaged across all four atlases, overlap was $M = 0.26$ ($SD = 0.03$) for DMN, $M = 0.24$ ($SD = 0.05$) for SN, and $M = 0.22$ ($SD = 0.04$) for FPN, compared to $M = 0.45$ ($SD = 0.05$) for the visual network; best-matching-atlas values ranged from $M = 0.37$ – 0.43 for the three networks of interest (single subject example in **Figure 1**), versus 0.61 for Visual. A permutation-based spin-test null model confirmed that every individualized network across all 38 participants exceeded chance correspondence to its best-matching atlas (all $ps < .01$).

To quantify agreement among the four reference atlases, we computed, for each subject and network, the ratio of overlap averaged across all four atlases to Dice overlap with the single best-matching atlas, where a ratio near 1 indicates perfect-convergence between definitions and a lower ratio indicates atlas-specific correspondence. This ratio was markedly lower for DMN ($M = 0.61$), SN ($M = 0.65$), and FPN ($M = 0.59$) than

Table 1 Sample characteristics for subjects included in brain-data analyses. 21 participants were taking only antidepressants at baseline, while 2 subjects were taking both antidepressants and antipsychotics.

Characteristic	Value
Subjects, N	38
Total scans/observations, N	181
Scans per subject, mean (SD)	4.76 (1.99)
Inter-scan interval (days), mean (SD)	127.26 (64.48)
Age at baseline (years), mean (SD)	16.16 (1.24)
Age at baseline, range	14.0–18.0
Sex, female, n (%)	28 (73.7%)
Sex, male, n (%)	10 (26.3%)
Study duration (days), mean (SD)	446.18 (172.35)
Study duration, range	129.0–851.0
Mean framewise displacement, mean (SD)	0.09 (0.03)
On antidepressants at baseline, n (%)	23 (60.5%)
On antipsychotics at baseline, n (%)	2 (5.3%)
Inpatient at baseline, n (%)	2 (5.3%)
Race: Asian	3 (7.9%)
Race: Biracial	3 (7.9%)
Race: Black	2 (5.3%)
Race: White	29 (76.3%)
Hispanic/Latino:	2 (5.3%)

for Visual ($M = 0.75$). **Figure 2** illustrates the between-person heterogeneity of FPN boundaries.

1.2 FPN connectivity shows state/trait dissociation in its association with depression severity

To understand the primary relationship between Mood and Feelings Questionnaire (MFQ) scores and RSN connectivity, we first extracted connectivity values from the subject-level ICA identified as being the most similar to the relevant canonical RSN (Tier 1; see **supplemental methods section 3.1.1**). Results from the within- and between-person mixed-effects models using primary IC connectivity estimates are presented in **Table 2**. When controlling for age, sex, duration of study participation, time-varying antidepressant medication use, subject random effects, and following FDR correction across the three *a priori* networks of interest, the FPN was the only network to show significant associations with MFQ-assessed depressive symptom severity at both the within- and between-person level ($qFDR < 0.05$).

At the between-person (*trait*) level, greater average FPN connectivity across scans was associated with significantly higher MFQ scores ($\beta = 2.07$, $SE = 0.781$, $q = 0.0239$). At the within-person (*state*) level, sessions in which an individual's FPN connectivity was higher than their own average were associated with significantly lower

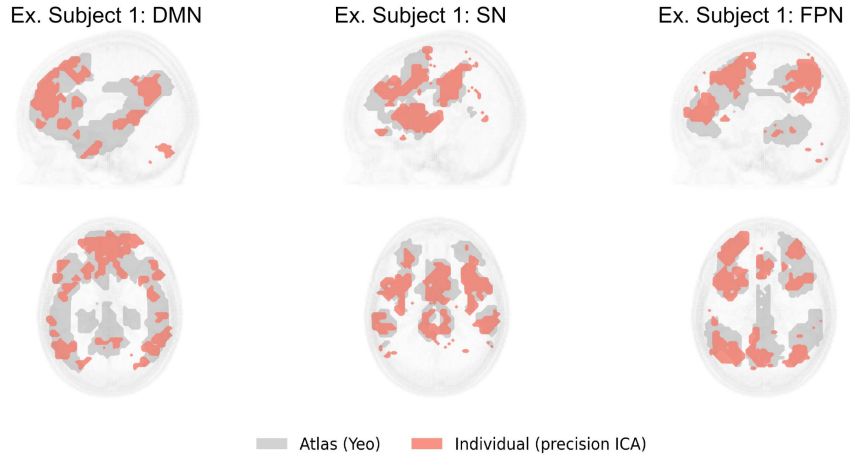


Fig. 1 Primary independent components assigned to the DMN, SN, and FPN compared to Yeo-Atlas definitions in an included subject. Masks were extracted from subject-level ICA, thresholded at the top 5% of loading values, and binarized. This replicates the same methodology used to establish the mask through which session-level connectivity values are extracted for each participant (discussed in **methods section 2.3.3**).

concurrent MFQ ($\beta = -0.6$, $SE = 0.283$, $q = 0.0356$). Raw bivariate relationships for FPN connectivity and MFQ are presented in **Figure 3**. Neither DMN nor SN connectivity was associated with MFQ at either the within- or between-person level (all $qFDRs > 0.05$) (see **Table 2**).

Table 2 Between-person and within-person effects of default mode network (DMN), salience network (SN), and frontoparietal network (FPN) connectivity and their associations with depression severity. Linear mixed-effects model results for within-network connectivity, primary IC only (Tier 1). Depression severity is assessed with the self-reported Mood and Feelings Questionnaire.

Network	Term	β	SE	t	p	CI Low	CI High	q (FDR)
DMN	Within	-0.304	0.260	-1.17	.244	-0.818	0.210	.291
DMN	Between	0.682	0.636	1.07	.291	-0.609	1.97	.291
SN	Within	-0.543	0.356	-1.53	.129	-1.25	0.161	.173
SN	Between	1.30	0.935	1.39	.173	-0.598	3.20	.173
FPN	Within	-0.600	0.283	-2.12	.036	-1.16	-0.041	.036
FPN	Between	2.07	0.781	2.65	.012	0.484	3.65	.024

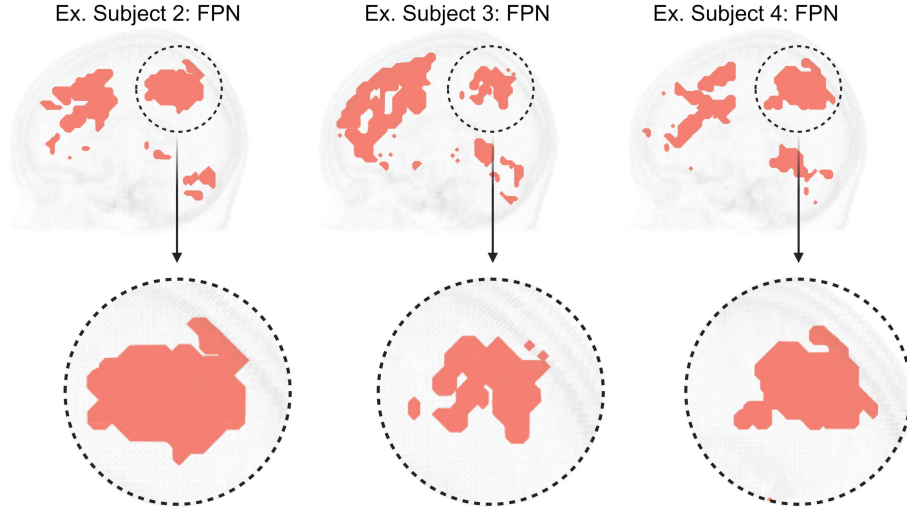


Fig. 2 Heterogeneous architecture of 3 included-participants' primary independent component assigned to the FPN. FPN spatial maps were extracted from 3 subject-level ICAs, thresholded at the top 5% of loading values, and binarized. This replicates the same methodology used to establish the mask through which session-level connectivity values are extracted for each participant (discussed in **methods section 2.3.3**). Enlarged circles highlight the heterogeneity of parietal activation between each subject's FPN. Subjects were randomly selected from the sample and maps are presented on the same slice of the glass brain template volume.

1.3 Comparison between individualized and atlas-derived connectivity results

To ensure that our brain-behavior associations were specific to personalized RSN definitions, we compared their results to network connectivity values derived using the popular Yeo 7-network atlas. We find that none of the atlas-based connectivity models yielded statistically significant associations with MFQ at either the within- or between-person level (all p s > .05, all q s > .05). Results using the personalized network definitions are presented alongside the atlas-based results in **Figure 4**. Atlas-based models produced standard errors approximately 5 to 10 times larger than their personalized equivalent, across networks and effect types, suggesting that group-average parcellations introduce significant noise into individual-level connectivity estimates.

Discussion

Within-person (*state*-related) and between-person (*trait*-related) connectivity may reflect distinct neurobiological processes relevant to depression; the former capturing transient, symptom-tracking fluctuations, the latter reflecting stable, illness-related vulnerability. Worryingly, this distinction has been conflated in the cross-sectional designs of prior research exploring adolescent depression. To test this distinction directly, we applied a novel pipeline to a cohort of densely sampled (181 scans from

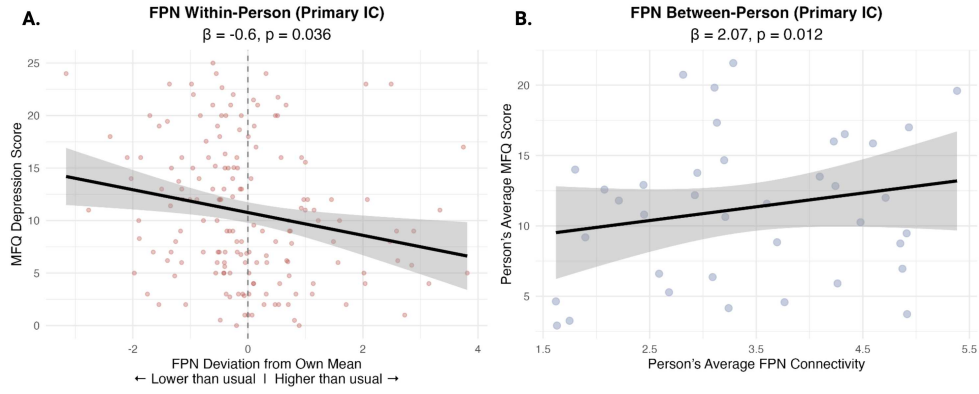


Fig. 3 State versus trait dissociation of connectivity of the frontoparietal network (FPN) with depression severity. Raw bivariate relationship for the (A) within- and (B) between-person level results, detailing the relationship between FPN connectivity and depression severity, as measured by the Mood and Feelings Questionnaire (MFQ). Dots in panel A) represent the within-person deviations in FPN connectivity from their own mean, compared to their concurrent MFQ score. Dots in panel B) represent participants' average FPN connectivity, compared to their average MFQ score. Statistics reported in the figure and in the main text control for age, sex, duration of study participation, and time-varying medication use.

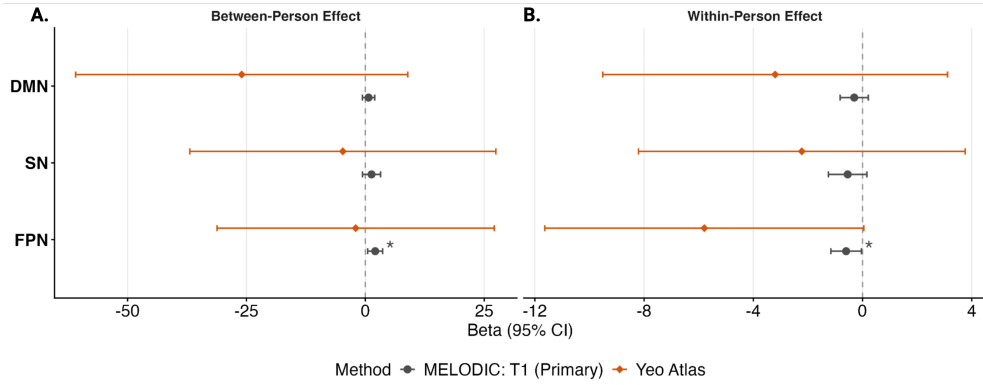


Fig. 4 Connectivity values derived from individualized functional maps are more precise than atlas-based analogues. Standardized beta coefficients across all models, tiers, resting-state networks and methods (Personalized versus Yeo). Panel A. details the between-person (trait) effect, while panel B. details the within-person (state) effect. Color denotes tier and method. DMN=default mode network; SN=salience network; FPN=frontoparietal network. † $p < 0.05$ (uncorrected), * $q(\text{FDR}) < 0.05$, ** $q(\text{FDR}) < 0.01$, *** $q(\text{FDR}) < 0.001$.

38 individuals) depressed adolescents to derive personalized RSN maps. Leveraging the improved sensitivity to individual differences and clinical translation relative to group-average approaches^{45,46}, our results revealed a significant *state-trait* dissociation within the FPN: *trait*-level (between-person) connectivity was positively associated with average depression severity, such that individuals with chronically higher FPN connectivity reported greater overall depressive burden, while *state*-level

(within-person) connectivity was negatively associated with concurrent severity, such that scan sessions with transiently elevated FPN connectivity corresponded to momentarily lower symptoms. This divergent pattern suggests FPN connectivity may reflect an effortful, *state*-dependent compensatory process that provides short-term symptom relief without resolving underlying *trait*-level vulnerability. SN and DMN connectivity, and all between-network connectivity metrics, showed no significant associations with depression severity (see **Supplement 3.1.2, 3.2.2**), indicating this dissociation is specific to within-network FPN connectivity.

Our results are consistent with a well-established literature characterizing the FPN as a locus of cognitive control. Anchored by the dorsolateral prefrontal and posterior parietal cortex, the FPN supports top-down regulation of emotional responses, suppression of ruminative-related DMN hyperconnectivity⁴⁷, and allocation of cognitive resources under affective challenge^{20,21,48}. Earlier work in understanding the FPN has connected its function to behaviors which are commonly impaired during MDD^{49–51}. More recent research has suggested that when the FPN fails to suppress DMN-mediated rumination, the result is the sustained negative mood characteristic of many depressive episodes^{17,52}.

These opposing *trait*- and *state*-level associations suggest FPN hyperconnectivity indexes two distinct facets of emotion regulation: a chronic, unsuccessful regulatory effort at the *trait*-level, and a transient, effective one at the *state*-level. Chronically elevated FPN connectivity in individuals with higher average depression burden may reflect a sustained compensatory attempt to regulate affective distress that is, on average, insufficient to prevent *trait*-level symptom accumulation⁵³. The momentary *state* effect, by contrast, may reflect brief windows of successful top-down regulation, in which the FPN suppresses rumination-related DMN activity and reorients cognitive resources⁵⁴. Clinically, this parallels the goals of Cognitive Behavioral Therapy (CBT) and repetitive transcranial magnetic stimulation (rTMS): not only suppressing activity in maladaptive circuits, but strengthening flexible regulatory engagement, even when average regulatory burden remains high, as in MDD^{55–57}.

Importantly, our results imply that depression cannot solely be characterized by global up- or down-regulation within key RSNs. Instead, depression may involve a remapping of the association between RSN dynamics and affective state: FPN hyperconnectivity signals vulnerability when sustained at the trait level and, simultaneously, adaptive regulatory engagement when elevated at the state level. This underscores the need for longitudinal, within-person designs to capture brain-symptom relationships in developmental psychiatric research, and cautions against treating cross-sectional connectivity differences as markers of illness versus health.

In comparison to our individualized results, none of the atlas-based, group-average models yielded significant within- or between-person connectivity-symptom associations for any of the three RSNs of interest, even the FPN. Atlas-based estimates also carried standard errors roughly 5–10 times larger than personalized estimates, reflecting greater uncertainty and attenuated effect sizes. Nonetheless, within-person effect directionality appears somewhat consistent with the personalized results, suggesting the atlas approach may measure some similar underlying signal that is being conflated

with other functionally unrelated regions. Recovering significant, theoretically coherent FPN effects only with individualized methodology supports adopting personalized neuroimaging in future longitudinal studies of adolescent psychopathology.

The most consequential methodological implication from these results concerns distinguishing within- from between-person effects. The FPN dissociation documented here would be obscured, and potentially sign-reversed, in a conventional cross-sectional analysis: a single-timepoint comparison would conflate two opposing signals into an estimate whose direction and magnitude depend arbitrarily on the sampled proportion of between- versus within-person variance. Cross-sectional analyses likely contribute to inconsistencies in the existing adolescent rsfMRI literature²³. The within- versus between-person decomposition framework^{10,11} resolves this by modeling each variance source explicitly, yielding more parsimonious and interpretable estimates. As longitudinal neuroimaging datasets in adolescent populations grow (e.g., Adolescent Brain Cognitive Development Study: ABCD), we argue that within- and between-person decomposition should become a standard analytic approach for brain measures expected to carry both stable, trait-like and dynamic, state-like information about a psychological construct.

In the present study, several limitations warrant mention. The sample size, while longitudinally dense (38 participants, 181 sessions), remains modest at the between-person level, limiting generalizability and raising the risk that significant trait-level associations reflect sample-specific variance. As the entire analytic sample met criteria for MDD, we could not conduct a case-control comparison and inferences regarding other forms of psychiatric illness (e.g., mania) could not be tested. The self-report MFQ captures overall MDD symptom severity but not distinct dimensions (e.g., anhedonia, somatic symptoms) likely associated with unique neural correlates. Scanner was excluded as a covariate because 180 of 181 scans were acquired on each participant's baseline scanner, making it nearly collinear with subject identity and redundant with the subject-level random effect. In the Yeo 7-network parcellation, the Ventral Attention Network (VAN) and SN are lumped together into a single unified spatial map. While the two networks are similar in their spatio-functional distributions, future work should seek to explore more specific definitions of these networks. This is particularly relevant in light of recent work that has indicated the “expansion” of the SN may be a trait-like biomarker of vulnerability depression⁵⁸.

Despite these limitations, this study demonstrates that personalized RSN mapping reveals a theoretically meaningful, clinically interpretable state-trait dissociation in FPN connectivity within adolescent depression. Critically, these findings were undetectable using atlas-based parcellations in the same sample. Chronically elevated FPN connectivity was associated with greater *trait*-level depressive burden, while transient within-person FPN increases co-fluctuated with concurrent symptom relief, suggesting the same substrate may index vulnerability at the *trait* level and regulatory capacity at the *state* level. Together, these findings suggest: (1) dissociating within-person from between-person effects should be a key analytic framework in longitudinal neuroimaging studies of adolescent psychopathology; (2) personalized functional network pipelines offer a measurable sensitivity advantage over atlas-based methods in developing, clinical cohorts. As personalized neuroimaging becomes more computationally

accessible and longitudinal adolescent psychiatric datasets grow, individualized RSN characterization represents a promising path toward reliable, person-specific neural biomarkers of *trait* versus *state* indicators of episodic mental illness, such as depression.

Methods

2.1 Sample

The Characterizing Adolescent Trajectories of Depression (CAT-D) study is a longitudinal neuroimaging investigation conducted at the National Institute of Mental Health (NIMH) designed to identify neural, behavioral, and clinical signatures associated with MDD onset, course, and treatment response in adolescents⁴⁴. The study recruited adolescents aged 12–19 with current or past diagnoses of a depressive disorder, as well as healthy volunteer (HV) participants, and followed them longitudinally across multiple assessment visits spanning the pre- and peri-COVID-19 pandemic period (2017-2022). Participants were recruited from the greater Washington, D.C. metropolitan area through community outreach, school-based referrals, clinical advertisements, and direct referrals from healthcare providers, with recruitment efforts emphasizing diversity in clinical presentation and demographic background. Adolescents provided written assent and their legal guardians provided written informed consent in accordance with protocols approved by the National Institute of Mental Health (NIMH) Institutional Review Board. All participants underwent a comprehensive battery of clinical interviews, self-report measures, and multimodal neuroimaging at the NIH Clinical Center in Bethesda, Maryland.

Clinical characterization included structured diagnostic interviews and self-report symptom measures administered at each visit (KSADS-PL according to DSM-5). Neuroimaging data were acquired using two 3T GE Signa MR750 scanners (GE Medical Systems, Milwaukee, WI) with 32-channel head coils, and included resting-state fMRI (rsfMRI), T1- and T2-weighted structural MRI, and task-based fMRI paradigms probing reward processing, emotion regulation, and cognitive control. Resting-state data were acquired using a multi-echo T2*-weighted echo-planar sequence (4 echoes: TE = 15.2, 28.8, 42.4, and 56 ms; TR = 2.5 s; flip angle, 80°; 32 oblique axial slices, 4.0 mm thickness; 64 × 64 matrix; field of view, 240 mm; in-plane resolution, 3.75 × 3.75 mm), lasting 8 minutes per acquisition; participants were instructed to remain still with eyes open for the duration of the scan⁵⁹. Data from the CAT-D study are made publicly available through the NIMH Data Archive (NDA; <https://nda.nih.gov>).

The primary symptom outcome for the present study was the self-reported Mood and Feelings Questionnaire (MFQ⁶⁰), a well-validated 33-item measure of depressive symptom severity in children, adolescents, and young adults (short MFQ). The MFQ was administered at each visit concurrently with neuroimaging, enabling within-person modeling of brain-symptom covariation across sessions.

Given the personalized neuroimaging approach employed here, inclusion in the present analyses required that each participant had: (1) a minimum of three rsfMRI sessions, and (2) all included sessions meeting motion quality thresholds described in **methods section 2.2**. These criteria reflect the minimum longitudinal data density required for stable within-person decomposition of brain-symptom associations.

2.2 MRI scan acquisition and Preprocessing

The rsfMRI preprocessing pipeline implemented in this study builds on that described previously by Ho et al.⁶¹. All data were visually inspected prior to preprocessing to assess for magnetic field inhomogeneities or disruptions in the scanner signal. Data were preprocessed using fMRIPrep (v24.0⁶²), which performed skull-stripping and cortical surface reconstruction via FreeSurfer's recon-all routine (v7.3⁶³), slice-time correction, and volume-based spatial normalization to the MNI 2 mm³ asymmetric pediatric template (MNIPediatricAsym; ANTs⁶⁴). Given the multi-echo acquisition, the four echoes were combined into a single optimally-weighted time series via fMRIPrep's echo combination procedure⁶⁵, which was carried forward as the preprocessed BOLD signal for all subsequent steps. fMRIPrep additionally generated framewise confound estimates, including six-parameter rigid-body motion parameters and mean CSF and global signal (GS) timeseries, for use in the nuisance regression described below.

Following fMRIPrep, additional post-processing was applied to the optimally-combined BOLD timeseries. Data were de-spiked (AFNI 3dDespike⁶⁶) and physiological correction was applied (RETROICOR⁶⁷), then spatially smoothed using a 5 mm full width at half maximum Gaussian kernel (fslmaths⁶⁸). Preprocessed data were then entered into a voxel-wise generalized least squares regression (fslregfilt) to filter out spurious activation related to physiology and motion by including the mean CSF timeseries, mean GS timeseries (along with 3 GS derivatives), and 24 motion parameters (3 translational, 3 rotational at each time point and the prior time point, and each of these 12 motion parameters squared) as nuisance regressors. The resulting residuals were bandpass filtered ($0.009 < f < 0.08$ Hz; fslmaths), de-meant (fslmaths, Tmean), and masked (fslmaths, -mas function) for use in subsequent analyses. For each subject, we computed mean relative displacement (MRD, also known as framewise displacement⁶⁹). Excessive movement was defined as having more than 20 volumes with a MRD > 0.25 mm and a mean MRD > 0.2 mm (no less than 85% low-motion volumes). 220 participants were removed due to exceeding motion thresholds and/or not having enough available scan data, resulting in an analytic sample of 38 depressed adolescents (73.7% female), contributing a total of 181 resting-state fMRI sessions (mean $\pm$ SD = 4.76 ± 1.99 scans, range: 3–11 scans).

All 38 participants were diagnosed with current MDD, whereas the majority of the whole CAT-D sample was characterized by HV participant data. At baseline, 21 participants were taking antidepressant medication only, and 2 participants were taking both antidepressants and antipsychotics. Of the 181 rsfMRI sessions, 168 had concurrent MFQ data available and were included in brain-symptom analyses. Full details of sample characteristics can be seen in **Table 1**.

Scanner assignment was stable within participants across the study; only 1 of 181 rsfMRI sessions ($<1.0\%$) involved a scan on a different scanner than the one used at the participant's initial visit, which was removed from all brain-symptom analyses. Participants were scanned at various intervals during their participation in the study, details of which can be seen in **supplemental Figure 1**.

2.3 Personalized RSN pipeline

A core contribution of the present study is the implementation of a subject-specific RSN extraction and analysis pipeline designed to overcome the limitations of group-average parcellation approaches when applied to developing clinical samples. Rather than projecting each participant's data onto a shared spatial template, the pipeline derives individualized RSN spatial definitions from each subject's own resting-state data, validates these components against canonical network templates using a principled scoring system, and then extracts session-level functional RSN metrics via dual regression. The following subsections describe each stage of this pipeline in detail. A visual stepwise breakdown of the pipeline can be seen in **supplemental Figure 2**.

2.3.1 Subject-level MELODIC ICA

Subject-level independent component analysis (SICA) was performed on each participant's concatenated rsfMRI data using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components⁷⁰), implemented in FSL. Unlike conventional ICA approaches that estimate a single shared spatial decomposition for a whole group, SICA runs directly on each individual's data. This yields a set of spatially independent components (ICs) that reflect that specific person's unique functional network architecture.

For each participant, all available preprocessed rsfMRI sessions were temporally concatenated prior to ICA decomposition, using the `-concat` flag in MELODIC. This concatenation approach ensures that the SICA decomposition captures stable, cross-session functional organization rather than session-specific noise fluctuations, and maximizes the temporal degrees of freedom available for component estimation. The number of components selected was based on previous work using MELODIC on an adolescent cohort with depression⁶¹, ensuring each participant's SICA output was the same dimensionality. The resulting SICA decomposition produced 25 component spatial maps (i.e., 25 ICs), per subject, which served as input to the subsequent RSN classification.

2.3.2 RSN Classification Using Network Correspondence Toolbox (NCT)

A fundamental challenge in any personalized pipeline is determining which subject-level maps correspond to canonical RSNs of interest, allowing for inter-subject comparison. This is particularly complicated because SICA spatial topographies and orderings vary substantially across individuals (see **Figure 2**). To address this, we used the Network Correspondence Toolbox (NCT⁷¹) in order to evaluate the spatial correspondence between each IC and a set of reference canonical network templates derived from established group-level atlases.

For each IC, the NCT computed a Dice similarity coefficient quantifying spatial overlap with each network label in each reference atlas, along with an associated permutation-based p-value reflecting the statistical significance of that overlap. Statistical significance was assessed using a spin-test null model⁷² implemented via the `SpinPermutations` function in BrainSpace: each individualized network map was

projected onto the fsaverage6 cortical surface and randomly rotated 1,000 times to generate a null distribution of Dice overlap values, an approach that preserves the spatial autocorrelation of the original map and avoids the inflated significance that a naive (non-spatial) permutation test would produce given the non-independence of neighboring cortical vertices. In the present study, correspondence was assessed against four reference atlases: the Yeo 7-network parcellation (TY7²⁶), the Yeo 17-network parcellation (TY17²⁶), the Schaefer 400-node 17-network parcellation (AS400Y17²⁸), and the Eickhoff-Grefkes 17-network parcellation (EG17⁷³). These atlases were selected to span a range of spatial resolutions (from the coarse 7-network solution to finer 17- and 400-parcel subdivisions) and were derived using distinct clustering methodologies and independent datasets, so that convergent IC-to-network correspondence across atlases could not be attributed to shared parcellation assumptions or a common underlying dataset. This multi-atlas approach reduces reliance on any single reference parcellation and captures cross-atlas consistency as a signal of network correspondence.

To synthesize correspondence evidence across atlases and networks into a single comparable score, we developed a composite scoring system. For each subject's IC-network pair, matching rows across atlases were identified using predefined label-to-network mappings (e.g., "Default," "DefaultA/B/C," and "Default" in TY7, TY17/AS400Y17, and EG17 respectively for the DMN). A weighted correspondence score was computed as the mean across matching atlas rows of $(1 - p\text{-value}) \times \text{Dice}$ plus a consistency bonus of 0.1 per distinct atlas in which the IC showed at least one matching label, rewarding cross-atlas convergence. ICs were required to meet a minimum Dice coefficient of 0.2 (20% overlap) and a maximum permutation p -value of 0.05 in at least one matching atlas row to be considered a viable candidate for a given RSN. This threshold was selected empirically based on the observed distribution of Dice coefficients in the present sample, chosen to balance retaining a qualifying candidate IC for every participant against minimizing the inclusion of spuriously matched components. The IC achieving the highest composite score for each target RSN was assigned as that network's primary representative IC. Based on prior meta- and mega-analytic literature investigating intrinsic functional network dysfunction in adolescent depression^{14,23}, the three networks of interest in the present study were the DMN, SN, and FPN. Each subject's primary representative IC for these three RSNs was then thresholded (top 5%) and binarized to create a subject-specific binary RSN mask, which served as the spatial window for subsequent dual regression metric extraction.

2.3.3 Obtaining session-level data using MELODIC Dual Regression (DR)

To extract session-specific functional RSN metrics from each participant's individual scan sessions, we used dual regression (DR⁷⁴), a two-stage procedure that uses the SICA's session-agnostic spatial maps to derive their session-level functional estimates.

In the first stage (DR Stage 1), each session's preprocessed BOLD data were projected onto the SICA spatial maps using ordinary least squares regression, yielding a set of session-specific timecourses (one per IC) representing the temporal dynamics of each network within that session. In the second stage (DR Stage 2), these session-specific timecourses were used as regressors against the original BOLD data,

producing session-specific spatial maps reflecting the voxel-wise contribution to each IC's timecourse within that given session.

Each component within the session-specific DR results corresponds to its "parent" component within the SICA (i.e., SICA DMN = DR DMN), but its functional topography varies from session to session. These session-to-session fluctuations in network expression constitute our primary predictor of interest. To quantify them, we extracted within-network RSN connectivity: the mean DR Stage 2 value across all voxels inside each subject's personalized RSN mask (derived in **methods section 2.3.2**). RSN connectivity reflects the degree to which a session's BOLD signal within the network's individualized spatial footprint co-varies with that network's canonical timecourse, a within-network functional integrity metric that captures both the spatial extent and signal quality of network expression within a given session. Higher connectivity values indicate more tightly coupled BOLD signals within the network mask, reflecting greater within-session functional integration of that RSN. Session-level connectivity values were extracted separately for the DMN, SN, and FPN, yielding three estimates per session per participant that served as the primary predictors in subsequent analyses.

2.4 Comparison with Atlas-Based connectivity Values

To evaluate whether the personalized ICA pipeline produced results substantively different from those obtained using conventional atlas-based methods, we implemented a parallel non-personalized connectivity extraction pipeline using the Yeo 7-network parcellation atlas²⁶. This atlas was retrieved programmatically via the Nilearn Python library⁷⁵ and resampled from MNI152 to the MNIPediatricAsym 2mm isotropic space used in preprocessing (described in **methods section 2.2**) using nearest-neighbor interpolation to preserve integer network labels.

For each session and each RSN of interest, a binary mask was created by isolating all voxels assigned to the corresponding Yeo-network label: label 7 (Default Mode Network) for the DMN, label 4 (Ventral Attention Network/Salience) for the SN, and label 6 (Frontoparietal Control Network) for the FPN. The mean BOLD timeseries across all in-mask voxels was computed, yielding a single canonical network timeseries per session. Network connectivity was then quantified by computing the Pearson correlation between each voxel's timeseries and this canonical mean timeseries, and averaging the resulting correlation values across all in-mask voxels. This mean voxel-to-network correlation served as the session-level, atlas-based connectivity estimate for each RSN; an analog to the ICA derived connectivity in our personalized methodology.

The same within-person/between-person decomposition and mixed-effects modeling framework described in **section 2.5** was applied to these atlas-based connectivity estimates, enabling direct comparison of effect sizes, significance, and directionality between the personalized ICA and atlas-based approaches. It should be noted that the atlas-based approach makes two assumptions explicitly avoided by the personalized pipeline: that all participants share an identical network spatial topography, and that the adult-derived Yeo parcellation adequately represents RSN boundaries in an adolescent clinical sample.

2.5 Statistical Approach

To examine how *state*- and *trait*-level RSN connectivity related to concurrent depressive symptom severity, we implemented a series of linear mixed-effects models using the *lme4* package⁷⁶ in R (R Core Team, 2024). For each network of interest (DMN, SN, FPN), session-level connectivity was decomposed into two analytically distinct predictors following the within-person/between-person centering approach described in Curran and Bauer¹⁰ and Bolger and Laurenceau¹¹.

The between-person (*trait*) predictor for each RSN was operationalized as each subject's mean connectivity across all available sessions ($\{\text{RSN}\}_{\text{mean_subj}}$), reflecting their stable, time-averaged level of network functional integrity. The within-person (*state*) predictor was operationalized as the session-level deviation from that subject-specific mean ($\{\text{RSN}\}_{\text{dev}} = \text{observed connectivity} - \{\text{RSN}\}_{\text{mean_subj}}$), capturing momentary fluctuations in connectivity above or below each individual's own baseline. Decomposing the predictor in this way ensures that the within-person effect estimates the association between transient changes in connectivity and concurrent symptoms within individuals, while the between-person effect estimates the association between stable individual differences in average connectivity and average symptom burden; two theoretically and statistically distinct questions that a single observed-score predictor would conflate¹⁰.

The outcome variable used in our modeling was the total MFQ score at each session. Fixed-effect covariates included days since first scan (mean-centered within subject to remove linear time trends), age at visit, sex (coded numerically), and current antidepressant use (time-varying binary, on/off). A random intercept for subject ID was included to account for the non-independence of repeated observations within individuals. Scanner ID was examined as a potential covariate but was excluded from final models due to complete collinearity with subject identity (all 38 participants were scanned exclusively on one of two scanners, with a single outlier scan removed from the dataset), which would have rendered the between-person RSN effects uninterpretable by absorbing between-subject variance.

For each RSN, the following model was estimated:

$$\text{MFQ}_{ti} = \beta_0 + \beta_1 \text{RSN}_{ti}^{\text{within}} + \beta_2 \text{RSN}_i^{\text{between}} + \beta_3 \text{Days}_{ti} + \beta_4 \text{Age}_{ti} + \beta_5 \text{Sex}_i + \beta_6 \text{Antidepressant}_{ti} + u_i + \varepsilon_{ti}, \quad (1)$$

where $u_i \sim \mathcal{N}(0, \sigma_u^2)$ is the random intercept for subject i and $\varepsilon_{ti} \sim \mathcal{N}(0, \sigma_\varepsilon^2)$ is the residual at session t .

$$\text{RSN}_i^{\text{between}} = \frac{1}{T_i} \sum_{t=1}^{T_i} \text{RSN}_{ti}, \quad (2)$$

$$\text{RSN}_{ti}^{\text{within}} = \text{RSN}_{ti} - \text{RSN}_i^{\text{between}}. \quad (3)$$

Models were estimated using restricted maximum likelihood (REML = TRUE) to obtain unbiased variance component estimates. Statistical inference was based on

Satterthwaite-approximated degrees of freedom as implemented in the *lmerTest* package⁷⁷. For each network, false discovery rate (FDR) correction was applied to the two primary tests of interest: the within-person and between-person connectivity effects for each R. Covariate effects were not included in the FDR correction family. An identical modeling framework was applied to the atlas-based connectivity estimates derived from the Yeo parcellation to enable direct comparison of personalized and non-personalized results.

Declarations

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- **Competing interests:** None to declare.
- **Data availability:** CAT-D data are openly available for download at <https://openneuro.org/datasets/ds004627/versions/1.1.1>.
- **Code availability:** Pre- and post-processing code for rsfMRI data, as well as the full individualized ICA RSN pipeline are available at https://github.com/jasperandrelaca/SICA_pipeline
- **Author contributions:** J.L., A.O., and T.C.H. conceptualized the initial study design. J.L. conducted data curation, created data methodology and software, conducted formal analysis and visualization, and wrote the original draft. A.O., conducted initial data curation. T.C.H. supervised. M.M.H. contributed methodology visualization. A.O., T.C.H., M.M.H., A.M., A.S.K., and L.Q.U. critically evaluated and revised the paper.

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Supplementary Information

3.1 Supplementary Methods

3.1.1 Addressing Component Fracturing

A recognized phenomenon in ICA decompositions is the fragmentation of canonical RSNs across multiple ICs; a pattern sometimes referred to as RSN fracturing or component splitting. Rather than yielding a single clean component for a given RSN, ICA frequently produces two or more spatially distinct components that each show significant correspondence with the same canonical RSN template. Whether this fragmentation reflects genuine individual differences in functional network architecture or represents a statistical artifact of ICA's component coercion remains an active area of investigation^{78,79}. Importantly, however, the behavioral and clinical relevance of RSN fragmentation is not purely theoretical. Prior work has demonstrated that ICA-derived DMN and SN subnetworks show dissociable relationships with suicidal ideation and non-suicidal self-injury in depressed adolescents, with connectivity deficits in these networks predicting distinct clinical presentations^{61,80,81}.

In the present study, we observed widespread RSN fragmentation across participants: the majority of subjects yielded multiple ICA components with significant spatial correspondence to the DMN, SN, and FPN, even after applying conservative candidate thresholds (Dice ≥ 0.3 , $p \leq 0.05$; see Section 2.3.2). To account for this, we implemented a three-tiered averaging approach to RSN connectivity extraction. In Tier 1, connectivity was computed using only the primary winning IC for each network, consistent with conventional single-component approaches and providing a baseline estimate. In Tier 2, connectivity was computed as the mean of the primary and secondary IC values for each network, where the secondary IC was defined as the next-highest-scoring qualifying candidate following global bipartite matching to resolve cross-network IC conflicts (see below). In Tier 3, connectivity was computed as the mean across all available qualifying ICs per network (primary, secondary, and tertiary, where present). For subjects with only one qualifying IC for a given network, higher-tier estimates fell back to the primary value, preserving full sample inclusion across all three tiers. This tiered approach allowed us to directly evaluate whether accounting for RSN fragmentation altered brain-symptom associations, and to assess the robustness of our primary findings across connectivity estimation strategies.

To resolve conflicts arising when a single IC achieved the highest correspondence score for more than one target network simultaneously, we employed a global maximum-weight bipartite matching algorithm⁸² applied independently at each assignment tier. This approach jointly optimizes IC-to-network assignments across all three networks simultaneously, minimizing the total loss of match quality while ensuring that each IC is assigned to at most one network per tier. Tier-specific assignments were made sequentially, with previously assigned ICs excluded from subsequent tiers, ensuring that secondary and tertiary assignments drew from the remaining unassigned candidate pool.

3.1.2 Between-Network connectivity (BNC) Analysis

To assess whether the state-trait dissociation observed for within-network connectivity extended to between-network relationships, we conducted an analogous state/trait decomposed analysis of between-network connectivity (BNC) for each pairwise combination of the three networks of interest (DMN-SN, DMN-FPN, SN-FPN). For each network, a mean timeseries was extracted by averaging the voxelwise BOLD timeseries within that network's SICA-derived mask (as described in Section 2.4); BNC for a given pair was then computed as the correlation between the two networks' mean timeseries. As in the primary within-network analyses, BNC values were decomposed into within-person (state) and between-person (trait) components and modeled using the same mixed-effects framework (Section 2.5), substituting the pairwise BNC term for the within-network connectivity term. Models were run using both primary-component masks (analogous to Tier 1; details discussed in supplemental section 3.1.1) and combined primary+secondary masks (analogous to Tier 2).

3.2 Supplementary Results

3.2.1 Component Fracturing

For all subjects, the mean number of fractured components was 2.9, 2.8, and 2.1 for the DMN, SN, and FPN, respectively. The results of the three-tiered method discussed in **Supplemental Methods Section 3.1.1** can be seen in **Supplemental Table 2a and 2b**. Through the tiers, the primary results were not dramatically altered. At the between-person (trait) level, the FPN remained directionally consistent and significant across all three tiers (T1: $\beta = 2.07$, $q = .024$; T2: $\beta = 2.71$, $q = .007$; T3: $\beta = 2.62$, $q = .011$). At the within-person (state) level, the FPN effect was significant at Tier 1 ($\beta = -0.600$, $q = .036$) but weakened to a non-significant trend at Tiers 2 and 3 (T2: $\beta = -0.570$, $q = .104$; T3: $\beta = -0.694$, $q = .061$). The DMN's within-person effect remained non-significant across all tiers, and its between-person effect, while numerically larger at Tiers 2 and 3 than at Tier 1, did not reach significance at any tier (T1: $\beta = 0.682$, $q = .291$; T2: $\beta = 1.48$, $q = .181$; T3: $\beta = 1.28$, $q = .196$). Tiering had no marked influence on the SN effects, which remained non-significant and stable in magnitude across all three tiers.

Supplementary Table 2a Within-person (state) effects across fragmentation tiers.

Tier	Network	β	SE	t	p	q (FDR)
T1: Primary	DMN	-0.304	0.260	-1.17	.244	.291
T2: Primary+Secondary	DMN	-0.424	0.336	-1.26	.210	.210
T3: All ICs averaged	DMN	-0.470	0.362	-1.30	.196	.196
T1: Primary	FPN	-0.600	0.283	-2.12	.036	.036
T2: Primary+Secondary	FPN	-0.570	0.348	-1.64	.104	.104
T3: All ICs averaged	FPN	-0.694	0.367	-1.89	.061	.061
T1: Primary	SN	-0.543	0.356	-1.53	.129	.173
T2: Primary+Secondary	SN	-0.675	0.422	-1.60	.112	.151
T3: All ICs averaged	SN	-0.660	0.443	-1.49	.139	.155

3.2.2 Between-Network Connectivity Results

Across all three network pairs and both mask tiers, no within-person or between-person BNC effect reached statistical significance, nor survived FDR correction (all $q > .25$; **Supplemental Table 3**). Effect directions were broadly consistent between mask tiers for a given pair (e.g., DMN-SN within-person $\beta = -1.29$ [primary] and -1.08 [combined]), suggesting the null result was not an artifact of IC fragmentation, but effect magnitudes remained small relative to their standard errors throughout. Between-person BNC estimates in particular carried wide confidence intervals (e.g., DMN-FPN combined-mask between-person effect: $\beta = -3.55$, 95% CI $[-9.65, 2.55]$), reflecting limited power at the between-subjects level for pairwise network metrics in this sample size.

Supplementary Table 2b Between-person (trait) effects across fragmentation tiers.

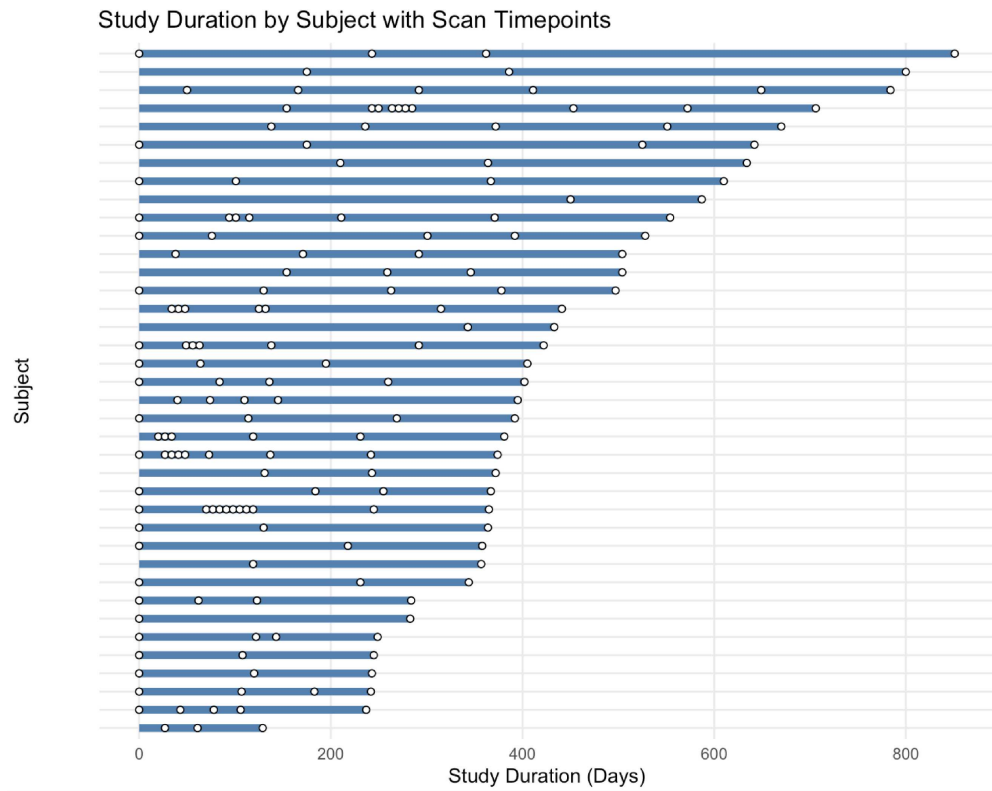
Tier	Network	β	SE	t	p	q (FDR)
T1: Primary	DMN	0.682	0.636	1.07	.291	.291
T2: Primary+Secondary	DMN	1.48	0.851	1.74	.090	.181
T3: All ICs averaged	DMN	1.28	0.901	1.42	.164	.196
T1: Primary	FPN	2.07	0.781	2.65	.012	.024
T2: Primary+Secondary	FPN	2.71	0.866	3.13	.003	.007
T3: All ICs averaged	FPN	2.62	0.888	2.95	.005	.011
T1: Primary	SN	1.30	0.935	1.39	.173	.173
T2: Primary+Secondary	SN	1.69	1.15	1.47	.151	.151
T3: All ICs averaged	SN	1.67	1.15	1.45	.155	.155

Supp. Table 3.

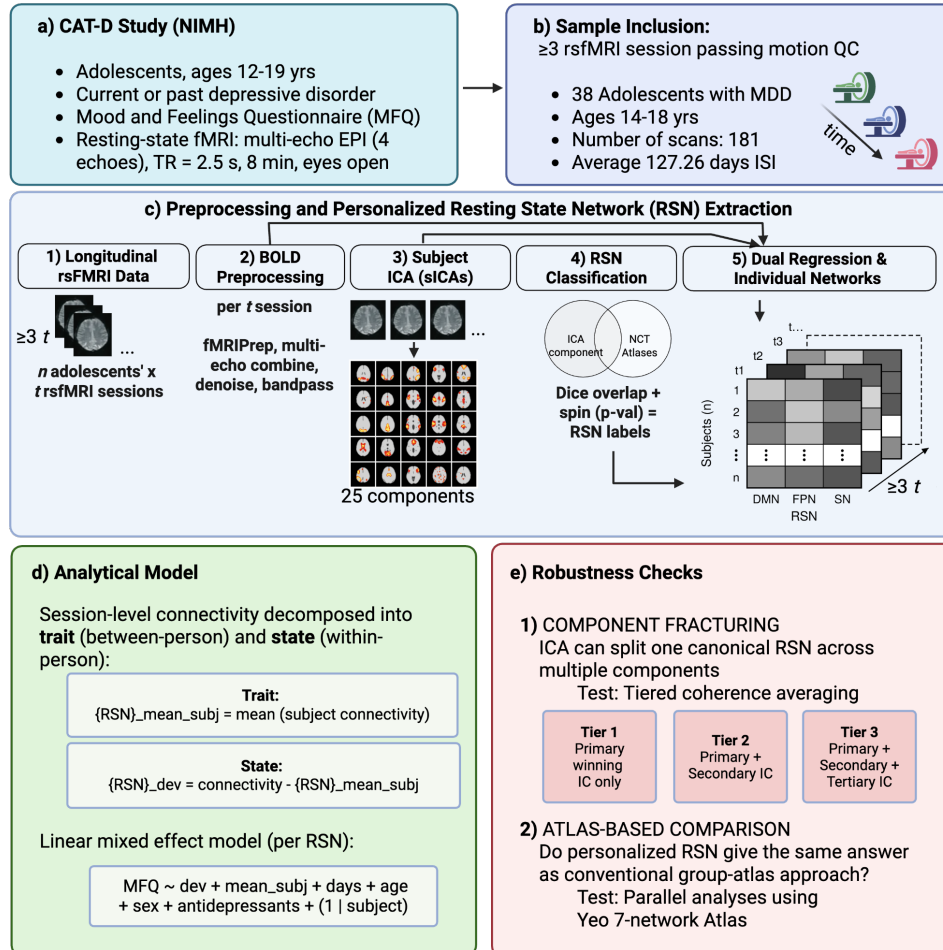
Supplementary Table 3 Within- and between-person associations in between-network connectivity and depressive symptom severity, by network pair and network-mask definition, show no significance.

Supplementary state/trait decomposition of between-network connectivity (DMN-SN, DMN-FPN, SN-FPN) across primary and combined mask tiers.

Pair	Mask	Term	β	SE	t	p	q (FDR)
DMN-SN	Primary	Within	-1.29	0.845	-1.53	.129	.258
DMN-SN	Primary	Between	-1.22	2.91	-0.42	.679	.679
DMN-SN	Combined	Within	-1.08	0.704	-1.53	.129	.257
DMN-SN	Combined	Between	0.15	2.95	0.05	.960	.960
DMN-FPN	Primary	Within	-0.82	0.938	-0.88	.382	.528
DMN-FPN	Primary	Between	-1.87	2.94	-0.64	.528	.528
DMN-FPN	Combined	Within	-0.78	0.803	-0.97	.333	.333
DMN-FPN	Combined	Between	-3.55	3.03	-1.17	.247	.333
SN-FPN	Primary	Within	-0.61	0.840	-0.73	.466	.932
SN-FPN	Primary	Between	0.08	3.27	0.02	.981	.981
SN-FPN	Combined	Within	-0.78	0.727	-1.07	.287	.575
SN-FPN	Combined	Between	1.04	2.71	0.38	.705	.705



Supplementary Fig. 1 Study duration and sampling within that duration for each participant. Each bar represents a participant, and each dot represents a sample point (e.g., rsfMRI and MFQ).



Supplementary Fig. 2 Stepwise pipeline breakdown, as described in Methods 2.3 and supp. Methods 3.1.1.