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Variation in moment-to-moment brain state engagement follows a consistent trajectory during development

Highlights

- Brain state engagement variability (SEV) shows a consistent developmental trajectory
- Female participants reach SEV stabilization before male participants
- SEV predicts executive function in previously unseen individuals
- Deviations from typical SEV development are linked to worse executive function

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In brief

Ye et al. demonstrate a consistent developmental trajectory for variability in recurring brain state engagement (SEV) across four independent datasets ($N > 3{,}000$). SEV increases with age before plateauing in adolescence, with female participants reaching stabilization before male participants. SEV further predicts executive function (EF) in previously unseen individuals.

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Variation in moment-to-moment brain state engagement follows a consistent trajectory during development

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SUMMARY

Neural variability, or variation in brain signals, facilitates dynamic brain responses to ongoing demands. This flexibility is important during development from childhood to young adulthood, a period characterized by rapid changes in experience. However, little is known about how variability in moment-to-moment brain state engagement changes during development. Such investigations would require the continuous assessment of multiple brain states concurrently. Here, we leverage a new computational framework to characterize the state engagement variability (SEV) developmental trajectory. A consistent pattern of SEV changing with age is identified across cross-sectional and longitudinal datasets (N > 3,000). The SEV developmental trajectory stabilizes around mid-adolescence, with timing varying by sex and brain state. SEV successfully predicts executive function (EF) in youth from an independent dataset. Deviations in SEV development are further linked to worse EF. These converging findings suggest that SEV changes over development, allowing individuals to flexibly recruit various brain states to meet evolving needs.

INTRODUCTION

Neural variability describes variation in brain signals.[1] Such fluctuations can be observed at multiple levels, ranging from variations in neuron spike intervals to interactions between large-scale brain networks.[2] Once considered a source of measurement noise, neural variability is now appreciated for its ability to support behaviors.[2,3] Specifically, higher neural variability may confer greater

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flexibility in exploring different brain network combinations to adopt the most optimal one for the task at hand.[2]

Given the significant neurodevelopment and executive function (EF) improvement during adolescence,[4–7] the role of neural variability is particularly crucial to consider during this critical life period. Perseverative behavioral patterns observed in younger children give way to the more flexible responses seen in older individuals.[8,9] Adolescence is additionally characterized by rapid changes in experiences and increased independence.[10] These changes can translate into a higher demand for flexibility to meet evolving needs. Increased neural variability may provide the flexibility needed to meet these unique challenges.

Emerging work has begun to tap the potential of neural variability in humans. Various forms of neural variability can be examined utilizing neuroimaging modalities, including electroencephalogram and functional magnetic resonance imaging (fMRI). These approaches span from assessing brain signal complexity with entropy[11] to evaluating variance (e.g., standard deviation or squared successive difference) in fMRI blood-oxygen-level-dependent (BOLD) signal[1,12,13] and functional connections over time.[8,14,15] Across studies, neural variability appeared to increase with age.[8,16–18] Importantly, elevated neural variability has been consistently linked to better EF performance in prior work.[1,12,16,19–21] These investigations suggest that increased variability allows the brain to flexibly recruit different brain networks to give rise to more adaptive behaviors in an increasingly complex world.

While these studies demonstrated the behavioral relevance of neural variability, the measures employed often focus on specific brain regions or networks.[3] Variability regarding recurring activity patterns across the whole brain (i.e., brain states) has received comparatively less attention. Accumulating evidence suggests the brain operates as a complex system where different brain regions coordinate with each other to give rise to behaviors,[22,23] necessitating a whole-brain approach. Multivariate, whole-brain approaches can additionally present more reliable findings on brain-behavior relationships.[23,24] The concept of brain states is also becoming increasingly popular,[25] leading to new understandings of the neural mechanisms underlying cognition.[14,26] Investigating variability in moment-to-moment brain state engagement thus presents the opportunity to study neural variability at the whole-brain level and gain new insights not available through previous metrics.

Recent work has begun to examine how adolescents transition from one brain state to another.[19] However, there is a lack of work examining variability in a given brain state's continuous engagement. Being able to interrogate each brain state individually is important for a number of reasons. Each brain state may recruit different brain networks to varying extents. Brain networks also develop at their own pace, often following a functional hierarchy.[27–29] Thus, examining each brain state separately may reveal subtle variations in its developmental trajectory or behavioral relevance.

Further, while many brain dynamic methods tend to characterize each time unit with the most dominant brain state, emerging work suggests that multiple brain states may occur simultaneously.[30,31] Focusing solely on the dominant brain state precludes the examination of less prominent ones when their variability may also support behavioral maturation. A method that can simultaneously quantify the continuous engagement

of multiple brain states is necessary to investigate the developmental trajectory and behavioral relevance of brain state engagement variability (SEV).

To address this gap, we capitalized on a new multivariate computational framework[32] that permits both temporal and spatial overlap in brain state engagement. Utilizing non-negative least-squares regression, this approach provides state engagement information at the resolution of individual time points for multiple brain states simultaneously. We leveraged this framework to estimate SEV in resting-state, naturalistic, and task-based fMRI from over 3,000 participants in two cross-sectional and two longitudinal developmental datasets. First, we characterized SEV's developmental trajectory by investigating whether age-related changes in SEV appear and generalize across paradigms. As sex differences in neurodevelopment exist,[33] we explored sex differences in SEV trajectory. Next, we explored the behavioral relevance of SEV by probing its relation with EF. We first used machine learning and external validation to predict individual differences in EF based on SEV. Next, by estimating brain age based on SEV, we asked whether larger deviations from typical SEV development would relate to worse EF performance at the time of data collection.

RESULTS

We first investigated SEV in two publicly available cross-sectional datasets, the Philadelphia Neurodevelopmental Cohort (PNC[34]) and the Healthy Brain Network (HBN[35]). Resting-state fMRI data from both datasets (PNC: N = 1,208, 658 females; HBN: N = 1,275, 491 females) were analyzed. We also included HBN's naturalistic fMRI data (N = 1,313, 505 females), collected while participants watched a clip from *Despicable Me*.

As both datasets were cross-sectional, we further validated our findings in two longitudinal datasets, the IMAGEN study[36,37] and the Michigan Longitudinal Study (MLS[38,39]). Task-based fMRI data collected during a cognitive control paradigm were analyzed (IMAGEN: stop signal; MLS: Go/NoGo). For the IMAGEN cohort, longitudinal fMRI data were collected from 530 participants (319 females) at 14, 19, and 23 years old. Two different MLS cohorts were used: one including 103 participants (40 females) aged 7.6 to 21.7 years old with 479 total visits (MLS cohort 1; visit distribution shown in Figure S1A), and the other comprising 150 participants (56 females) between 16.1 and 28.5 years of age with 639 total visits (MLS cohort 2; visit distribution shown in Figure S1B).

To assess SEV, we first implemented our established pipeline to identify four canonical brain states using nonlinear manifold learning and task-based fMRI data from the Human Connectome Project (HCP) dataset.[40,41] We used fMRI data from six tasks (motor, working memory, social, emotional, relational, and gambling). As this dataset included tasks ranging from motor to cognitive and affective paradigms, it has the potential to reveal brain states underlying a diverse set of cognitive processes. Additionally, identifying brain states in another dataset avoids circular analysis and overfitting. Based on their associated task conditions and demands (see STAR Methods), we labeled the identified brain states as fixation, high-cognition, low-cognition, and cue/transition. The fixation state mostly contained time points from the fixation condition. The high-cognition state included time points from complex cognitive paradigms such as working memory, emotion, relational, gambling, and social. The low-cognition state included many time points from the motor task. Finally, the cue/transition state mainly consisted of time points from the cue condition. The activation of canonical functional brain networks also followed the cognitive processes associated with each state. For instance, the high-cognition state showed frontoparietal network activation and default mode network (DMN) deactivation (see STAR Methods). The continuous engagement of these four brain states was evaluated in the PNC, HBN, IMAGEN, and MLS cohorts (Figure 1; for details, see Ye et al.[32]). SEV was operationalized as the standard deviation of moment-to-moment engagement across time. We performed false discovery rate (FDR) correction on all primary analyses with $q < 0.05$ considered as significant.

SEV increased with age across fMRI paradigms

In both PNC and HBN, we observed a positive association between age and SEV during resting-state and movie-watching (multivariate analysis of variance [MANOVA]; PNC rest: $F(4, 1{,}201) = 20.793$, $q < 0.001$; HBN rest: $F(4, 1{,}268) = 36.482$, $q < 0.001$; HBN movie: $F(4, 1{,}305) = 55.959$, $q < 0.001$). Post hoc correlations highlighted that this positive association can be found across states and cohorts (Figure 2). Nevertheless, these effect sizes demonstrated variations. Stronger effects were observed in HBN compared with PNC and in the movie condition compared with the rest condition. The high-cognition and fixation states showed the greatest effects out of all brain states examined.

Longitudinal changes in SEV

As cross-sectional data might not be sensitive to subtle developmental changes, we investigated longitudinal changes in SEV by applying linear mixed-effects (LME) models to longitudinal fMRI data. The IMAGEN dataset collected data at ages 14, 19, and 23. Fixation SEV was greater at ages 19 and 23 than at age 14 (Figure 3; Table S1). Interestingly, no significant age difference was found for the other SEVs after FDR correction (Figure 3; Table S1). SEV did not differ across all four states between ages 19 and 23 (Table S1). These results extended our previous cross-sectional findings, suggesting that during typical development, SEV does not increase indefinitely with age but stabilizes around mid-adolescence. Notably, this asymptote's timing may depend on the specific brain state.

2This possibility was further explored in MLS, which included multiple visits from some participants and allowed for the investigation of smoother trajectories. In the younger sample (MLS cohort 1; 7.6–21.7 years old), SEV increased with age across all states but low-cognition (fixation: beta = 0.028, $t(470.8) = 5.07$, $q < 0.001$; high-cognition: beta = 1.916e−02, $t(470.7) = 5.321$, $q < 0.001$; low-cognition: beta = 1.972e−03, $t(460.3) = 2.002$, $q = 0.14$; cue/transition: beta = 0.012, $t(468.9) = 3.670$, $q = 0.001$; Table S2 for other covariates). However, consistent with our prior observations in IMAGEN, SEV did not change significantly with age in the older sample (MLS cohort 2; 16.1–28.5 years old; LME; fixation: beta = −0.001, $t(584.6) = -0.246$, $q = 0.849$; high-cognition: beta = 0.0006, $t(580.3) = 0.191$, $q = 0.849$; low-cognition: beta = −0.0007, $t(590.4) = -0.771$, $q = 0.849$; cue/transition: beta = −0.002, $t(587.793) = -0.514$, $q = 0.849$; Table S2 for other

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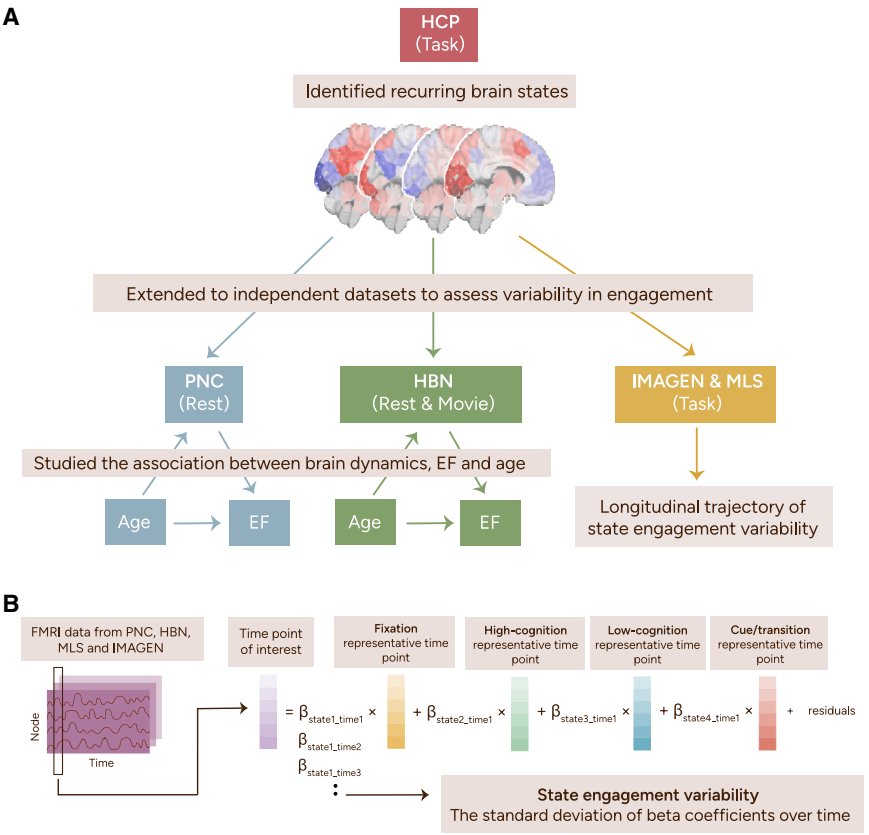

Figure 1. Study pipeline

(A) We identified four recurring brain states using task-based fMRI data from the HCP. These four brain states were then extended to the PNC, HBN, IMAGEN, and MLS datasets using a previously established pipeline shown in (B). To summarize, the representative time points from all four states were regressed from each time point from the PNC, HBN, IMAGEN, and MLS datasets using non-negative least-squares regression. This step returned a beta coefficient for each state, indicating its engagement at that time point. SEV was computed as the standard deviation of beta coefficients across time for each participant. Age distributions are shown in Figure S1C. HCP, Human Connectome Project; PNC, Philadelphia Neurodevelopmental Cohort; HBN, Healthy Brain Network; MLS, Michigan Longitudinal Study.

covariates). To visualize this developmental trajectory, we combined both MLS cohorts. These trajectories (Figure 4) suggest that SEV follows a nonlinear trajectory.

Observations across four independent datasets converged to paint a general pattern of SEV first increasing with age before stabilizing around mid-adolescence during typical development. This trajectory was found using fMRI data collected during rest and movie, as well as cognitive control tasks. Notably, specific stabilization timing may vary by brain state, with a brain state recruiting regions in the association cortex (i.e., fixation) reaching maturation last and a brain state recruiting mainly sensorimotor regions (i.e., low cognition) reaching maturation earlier.

Timing of SEV stabilization varied by self-reported sex

As previous work has noted sex differences in brain development, we further probed the effects of self-reported sex on SEV. A significant age-by-sex interaction was found in PNC (MANOVA; age-by-sex interaction: F(4, 1,201) = 3.838, q = 0.006; main sex effect: F(4, 1,201) = 1.133, q = 0.340) but not in HBN (MANOVA; rest: age-by-sex interaction: F(4, 1,268) = 0.54, q = 0.813; main sex effect: F(4, 1,268) = 1.884, q = 0.167; movie: F(4, 1,305) = 0.394, q = 0.813; main sex effect: F(4, 1,305) = 4.084, q = 0.006). However, age differences between the two datasets likely contributed to this discrepancy (two-sample t tests: $p < 0.001$; PNC age: 14.688 ± 3.321; HBN rest age: 11.693 ± 3.39; HBN movie: 11.361 ± 3.606). Compared with HBN, the PNC cohort included more participants in late adolescence. The age-by-sex interaction in PNC likely reflects potential group differences occurring later in development, perhaps when individuals reach the stabilization point previously noted in our longitudinal results (Figure 4).

In support of this hypothesis, we observed a significant interaction between sex and later visit on SEV across all four states in IMAGEN (LME; interaction between sex and visit at 23 years old; fixation: beta = 5.390e−02, t(1,056) = 3.429, q = 0.003; high-cognition: beta = 3.741e−02, t(1,056) = 3.609, q = 0.003; low-cognition: beta = 1.190e−02, t(1,056) = 3.928, q = 0.003; cue/transition: beta = 3.425e−02, t(1,056) = 3.496, q = 0.003; see Table S1 for interaction between sex and visit at 19 years old). These results provide further evidence of potential sex differences occurring in late adolescence.

We next probed whether there were sex differences in the timing of SEV peak by performing a post hoc analysis in the MLS dataset, which included dense sampling across various ages. The peak age was first identified for female and male participants (see STAR Methods; Table 1). The difference between females and males was then calculated. Next, peak age difference was recalculated 500 times after shuffling self-reported sex across participants. We subsequently determined the p value by counting the number of permutation tests yielding a larger difference than the observed value. Permutation testing revealed that female participants arrived at the peak age earlier for the fixation brain state ($p < 0.001$) but not for the other brain states (high-cognition: $p = 0.82$; low-cognition: $p > 0.999$; cue/transition: $p = 0.154$). It is important to note here that the two groups showed more overlap around the peak age for the other brain states (Figure 4), potentially contributing to the lack of sex differences observed.

SEV predicts EF in development

Our findings revealed a remarkably consistent pattern of SEV changing with age. As dramatic changes in experiences

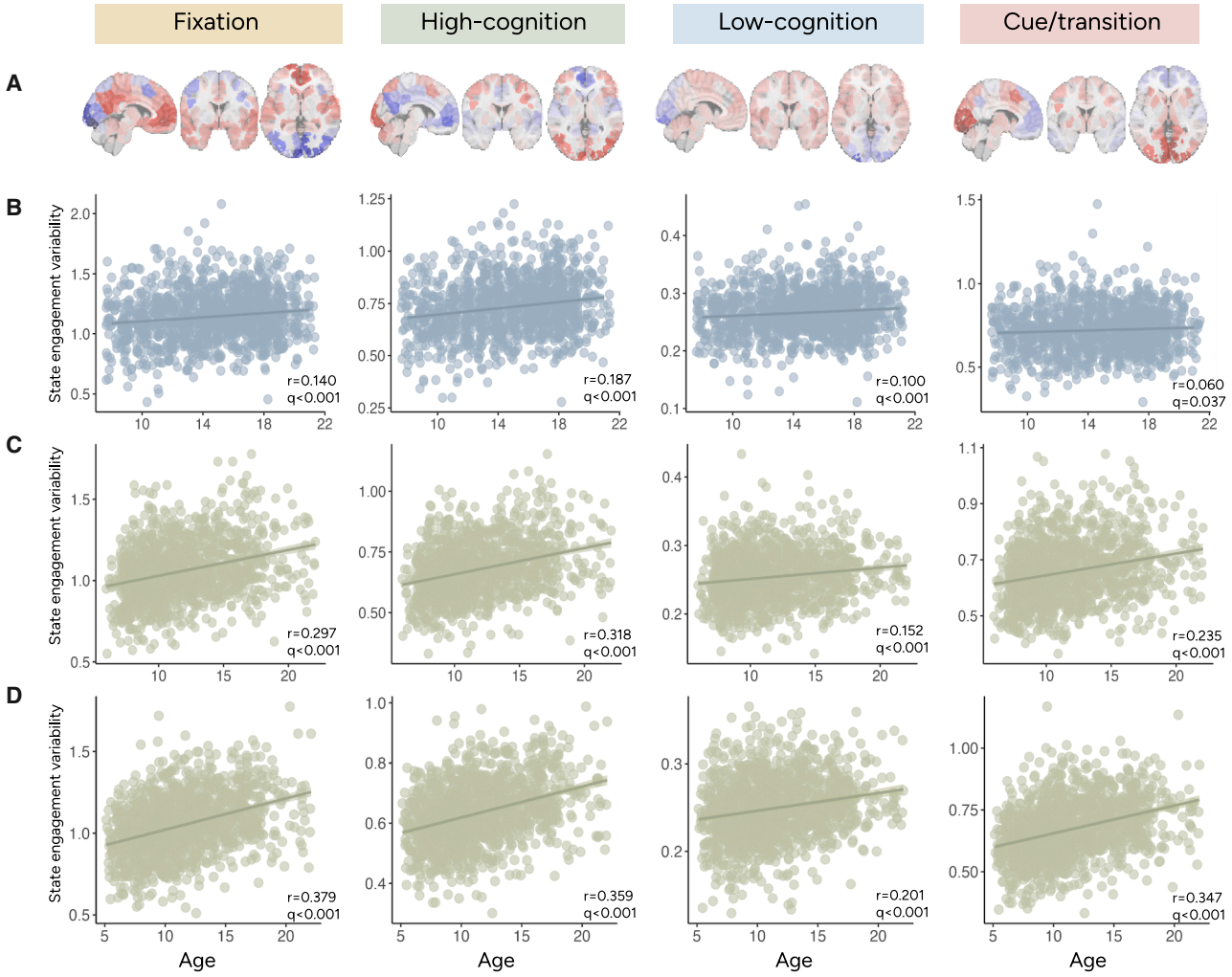

Figure 2. SEV increased with age in PNC and HBN

(A) shows the activation patterns associated with the fixation, high-cognition, low-cognition, and cue/transition brain states. Across all four brain states, we observed a positive association between age and SEV in PNC rest (B), HBN rest (C), and HBN movie (D). Results from Pearson's correlation between SEV and age are also reported here. Pearson correlations were performed as an exploratory analysis to characterize the direction of the relationship, and corrections for multiple comparisons were done within each dataset.

characterize development, one follow-up question is whether variations in SEV have any behavioral relevance. We investigated the association between SEV and EF in the two cross-sectional datasets. EF was evaluated using the NIH Toolbox and the Penn Computerized Neurocognitive Battery (CNB) in HBN and PNC, respectively. A summary EF score was extracted using principal-component analysis (PCA) on scores from the different EF tasks (see STAR Methods). In the PNC dataset, the 1st EF component accounted for 48.166% of the variance. The 1st EF component accounted for 65.379% and 68.205% of the variance in the HBN rest and movie cohorts, respectively.

We then examined whether SEV can predict EF in previously unseen individuals from an independent dataset. A linear model was trained to predict EF using SEV in either dataset before being applied to the other dataset. To keep the fMRI paradigm consistent in both the training and testing datasets, we analyzed the PNC and HBN rest cohorts. Predicted EF showed a significant positive correlation with observed EF (Pearson correlation; model tested in PNC: $r = 0.160$, $p < 0.001$; model tested in HBN: $r = 0.202$, $p < 0.001$). We successfully predicted EF with relatively few features included in the models (see model parameters in STAR Methods). Importantly, consistent results were obtained from two unharmonized datasets evaluating EF utilizing different tools. We additionally probed the association between SEV and EF using mediation analyses (see STAR Methods). Altogether, these findings suggested SEV was relevant for EF performance during typical development.

Increased brain age alteration was linked to lower EF performance

SEV's robust developmental trajectory also presented the opportunity to investigate whether alterations from typical SEV

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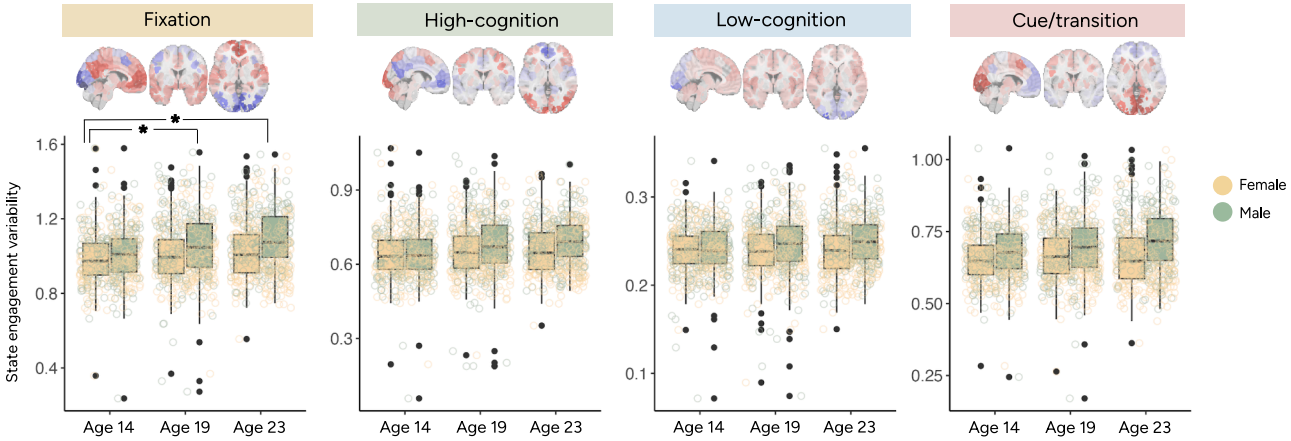

Figure 3. SEV in the IMAGEN dataset plotted by visit and sex

Data were collected at ages 14, 19, and 23. Ages 19 and 23 showed greater fixation SEV than those aged 14. However, no significant age difference was observed for the other brain states after correcting for multiple comparisons. Ages 19 and 23 did not differ significantly in SEV for any brain states examined (Table S1).

development related to individual differences in EF. We measured alteration from typical development by the squared difference between chronological age and brain age estimated from SEV. Larger alterations were interpreted as appearing younger (i.e., delayed development) or older (i.e., accelerated development) compared with one's peers regarding each individual's SEV profile. Like the previous analysis, linear models were trained to predict age with SEV in the PNC and HBN rest cohorts (see model parameters in STAR Methods). Brain age correlated significantly with actual age (tested in PNC: $r = 0.204$, $p < 0.001$; tested in HBN: $r = 0.269$, $p < 0.001$; Figure 5A). When controlling for chronological age, both datasets exhibited a significant negative correlation between brain age alteration and EF (tested in PNC: $r = -0.242$, $p < 0.001$; tested in HBN: $r = -0.27$, $p < 0.001$; Figure 5B). In the two cross-sectional datasets, larger deviations from typical SEV development were associated with lower EF performance at the time of data collection.

SEV trajectory remained consistent when controlling for covariates and constructing brain states in a developmental population

We presented converging evidence from four different datasets to characterize SEV's developmental trajectory. To further demonstrate the robustness of our findings, we reran our analyses while controlling for motion and intracranial volume (ICV). Consistent age effects were still observed when these covariates were included in the model (see STAR Methods). We further showed that age's effect on SEV remained consistent when controlling for variables assessing an individual's family and neighborhood environment as well as their physical and mental health (see STAR Methods). These validation analyses revealed that the

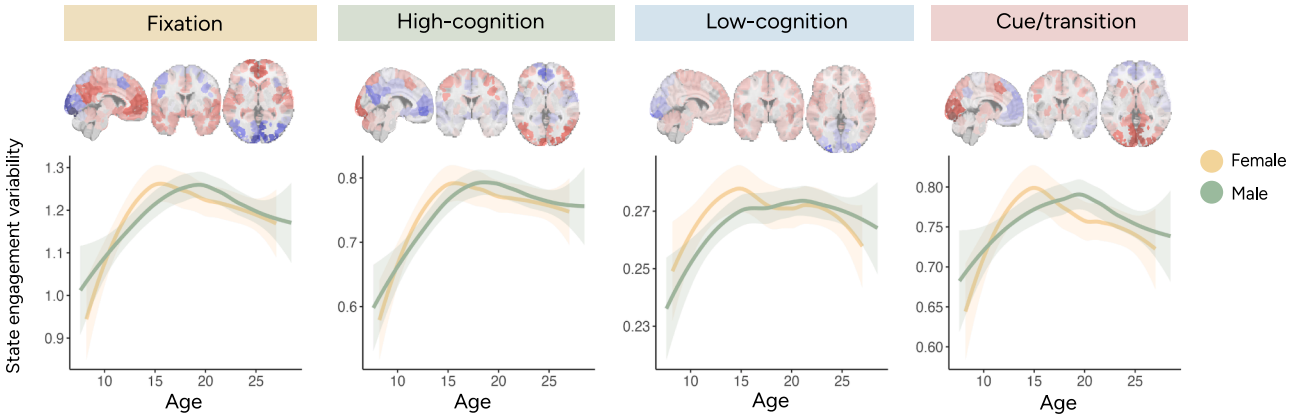

Figure 4. SEV trajectory plotted by sex using data from the MLS datasets

The smoothed curve was generated using the locally weighted least-square regression technique in R's ggplot2 package. Activation patterns associated with each brain state are again shown above the trajectories. Across all four brain states, SEV increased with age before reaching its peak in adolescence. Plotting trajectories by group additionally indicated that female participants appeared to reach a stabilization point before male participants. LME covariate results from analyses conducted within MLS cohorts 1 and 2 are shown in Table S2.

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Table 1. Age at transition point in SEV trajectory by sex (MLS)

	Fixation	High cognition	Low cognition	Cue/transition
Male	17.5764	15.8559	13.6781	17.4534
Female	16.0619	15.8555	13.6784	16.4343

relationship between age and SEV was unlikely to be driven by these covariates.

Here, we constructed brain states using the HCP dataset, which recruited young adult participants. One potential interpretation is that SEV's developmental trajectory reflects adolescents' brain states becoming more and more adult-like, instead of intrinsic neural flexibility increasing with age. To provide evidence for the latter, we reran our analyses using brain states identified in a developmental population (see STAR Methods). We focused specifically on the movie-watching HBN dataset, as naturalistic paradigms may invoke various cognitive processes. Consistent results were found using SEV derived from these brain states (see STAR Methods). It is worth noting that HBN participants were younger than those included in the IMAGEN and MLS datasets. Yet, we again observed a main effect of age and an age-by-sex interaction on HBN-derived SEVs in both longitudinal datasets (see STAR Methods). These findings strongly indicated that SEV's developmental trajectory reflects flexibility increasing with age to meet the increasingly complicated challenges during development, rather than an individual's brain state becoming more adult-like.

DISCUSSION

In over 3,000 participants, we identified a consistent developmental trajectory for variability in recurring brain state engagement. SEV's developmental trajectory was explored in four datasets covering slightly different age ranges. SEV increased with age in the younger PNC, HBN, and MLS cohort 1 participants. However, this growth did not continue indefinitely. Results from the older IMAGEN and MLS cohort 2 participants suggested that SEV plateaued in adolescence. Altogether, data from these independent datasets aligned to show a ubiquitous developmental trajectory characterized by an initial stage of age-related increase followed by a peak in mid- to late-adolescence. Consistent findings generalized across resting-state, naturalistic, and task-based fMRI paradigms, suggesting that changes in SEV characterize the developing brain. SEV predicted EF performance in previously unseen individuals and partially mediated the relationship between age and EF. Additionally, alterations from typical SEV development were related to lower EF performance. We present novel evidence to extend previous literature on how neural variability allows the brain to respond dynamically to increasingly complex demands during development.

Our findings echo previous work reporting increased neural variability in older adolescents and young adults.[8,16,17] While SEV increased with age in childhood and early adolescence, it stabilized around mid-adolescence. The initial growth of SEV

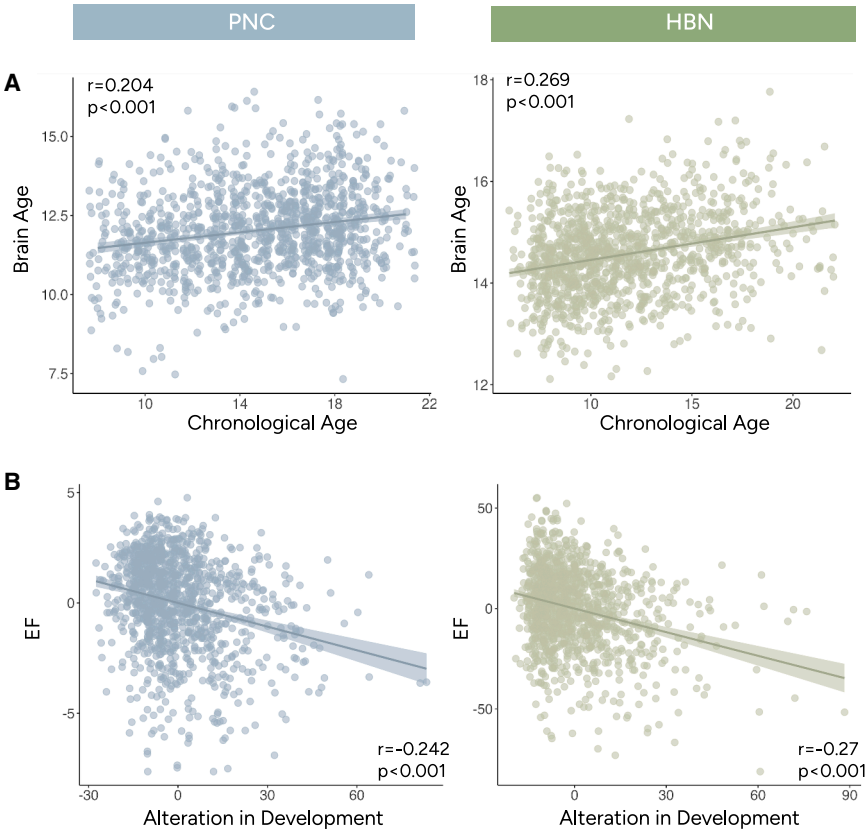

Figure 5. Age predictions using SEV measures

(A) Brain age predicted by SEV was significantly associated with chronological age.

(B) Individuals with SEV resembling someone older or younger showed worse EF performance. Age was regressed from both EF and SEV alteration before plotting. Instead of the actual values, residuals from the regressions were shown here to match our partial correlation analysis. Correlation results from PNC and HBN were shown in blue and green, respectively.

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may provide individuals with greater cognitive flexibility to support information processing, which is vital for increased exploration and enhanced learning about the changing world. However, future work is needed to investigate whether elevated SEV emerges naturally or serves as a response to the heightened variability in experiences during development.

The developmental trajectory of SEV demonstrated characteristics consistent with known trajectories of other brain measures. Importantly, tracking each brain state separately revealed subtle variations. Specifically, out of the four states examined, the low-cognition brain state reached stabilization the earliest, whereas the fixation brain state took the longest. The low-cognition brain state mainly engaged unimodal regions in the sensorimotor system. The fixation brain state recruited the DMN, which includes multimodal brain regions in the association cortex. Brain development follows a hierarchical axis from the sensorimotor system to the association cortex.[27–29,42] The earlier maturation in the low-cognition brain state coupled with the relatively later development in the fixation brain state dovetails with these observations.

Other neurobiological changes also occur during the same time as SEV growth. Across development, white matter tracts show increased myelination and axonal organization.[43–49] Synapse elimination also takes place at this time.[50,51] Notably, these neurobiological changes shared many characteristics with SEV development. Similar to SEV, these changes follow a sensorimotor-to-association-cortex axis[44–46,51–53] and stabilize in adulthood.[44,49] The significant overlap in developmental characteristics prompts the intriguing possibility that such neurobiological changes can influence SEV development. In particular, the strengthening of white matter tracts and synaptic pruning can increase signal fidelity, transmission speed, and signal-to-noise ratio.[4,44] Enhanced information processing and communication can allow for more efficient coordination and combination of dynamic whole-brain activation patterns, thus supporting SEV's age-related increase at the same time. Neurobiological changes can serve as an important foundation for guiding and constraining SEV development. Future studies should formally test this hypothesis by examining whether structural changes precede or can be used to predict later SEV development using longitudinal multimodal data.

We observed sex differences such that female participants appeared to reach the stabilization point before male participants for the fixation brain state. This finding aligned with prior evidence of sex-stratified developmental trajectories of both whole-brain and subcortical gray matter volume.[33,42] The later peaks in SEV in male participants also aligned with studies demonstrating similar lags in resting-state functional connectivity stability,[54] puberty emergence, as well as some elements of EF performance (e.g., impulse control[55]) in male adolescents. While we observed significant age-by-sex interaction in three of the datasets examined, future work using longitudinal or dense-sampling data is needed to validate our results on stabilization timing. Additional work can probe whether sex differences in peak timing affect the emergence of disorders with significant sex differences in prevalence.[56]

While this study focused on development, future work could investigate whether the trajectory follows an adolescent emergent (i.e., trajectory peaks at adolescence and stabilizes in adulthood[57]) or adolescent-specific trajectory (i.e., trajectory peaks at adolescence and falls in adulthood[57]). Our previous work found that SEV decreased with age in adult participants with and without psychiatric disorders.[32] These preliminary results suggest that SEV might follow an adolescent-specific or inverted-U-shaped trajectory. Additional research can test this hypothesis across the lifespan using nonlinear methods and probe its implications for EF changes in aging populations.

To test the reliability of SEV's developmental trajectory, we conducted control and sensitivity analyses to investigate whether the pattern we observed stayed consistent when different factors were considered. We performed secondary analyses on curated datasets. As a result, preprocessing varied across datasets, resulting in slightly different framewise displacement metrics being applied to participants from different cohorts. But results remained consistent when motion was included in the model (see STAR Methods). Variations during preprocessing may be a limitation from working with curated datasets. However, obtaining the same developmental trajectory using data acquired with different scanners and preprocessed with different pipelines demonstrated the generalizability and replicability of our results.[58]

Secondly, we identified a reliable developmental trajectory for SEV using fMRI data collected during rest, movie, and cognitive control tasks. The consistent result across datasets indicated that SEV's developmental trajectory is robust to fluctuations in brain activity or alertness during scan. Interestingly, we did not observe consistent intrinsic changes in the amount of brain state engagement across age (see STAR Methods). The significance of this finding is 2-fold. First, it suggests changes in SEV were different from intrinsic brain activity changes occurring during development.[29] Secondly, if the HCP-derived brain states were a better match for the older participants, we would see the amount of brain state engagement increasing consistently with age. However, we did not observe this pattern. The lack of association between intrinsic brain state engagement and age, along with our control analysis with HBN-derived brain states, indicated that the trajectory we observed likely reflects increased neural flexibility during typical development.

Lastly, we explored whether age-related changes in SEV remained significant when we controlled for variables assessing an individual's family and neighborhood environment as well as their mental and physical health (see STAR Methods). Age's effect on SEV stayed robust when these covariates were included in the model. But factors not considered in this study (e.g., family or genetic risks) may influence SEV and alter its development. Investigating how these variables can potentially change developmental trajectory and influence behaviors using longitudinal data is an exciting direction for future research.

Here, we provided several lines of evidence to establish a link between SEV and EF. Higher SEV was related to better EF performance. Additionally, SEV predicted EF in previously unseen individuals. These findings are consistent with prior literature showing a positive relationship between neural variability and faster, more accurate, and more stable performance in a range of tasks.[1,12,16,19,20] As these associations were found between behaviors collected outside the scanner and brain dynamic

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measures extracted from resting-state, naturalistic, and task-based fMRI, SEV likely serves as an index for intrinsic flexibility with behavioral relevance.

A natural conclusion from these results is that higher SEV is associated with better cognition during typical development. However, our exploratory analysis suggested that the on-time development of SEV is also essential, with accelerated and delayed SEV development linked to lower EF performance scores at the time of data collection. This Goldilocks effect was observed in two independent datasets with external validation. Accelerated and delayed neurodevelopment have been associated with various risk factors, including parental deprivation, low socioeconomic status, preterm birth, childhood abuse, and stress.[59–63] Factors such as social structure, community violence, and marginalization, which can be harder to measure, can also play a role in brain development.[64] Delineating how SEV interacts with these environmental and risk factors remains an important future direction.

Alterations from typical development may also be adaptive in ways not captured by the EF tasks. Such alterations may manifest as an adaptive response developed in the context of adversity exposure.[65,66] For instance, youth may develop accelerated SEV to cope with the demands of stress or trauma exposure. In the case of accelerated development, while higher variability may increase noise and hinder the distinction between meaningful and irrelevant stimuli during an EF task, it may facilitate more rapid responses in an unpredictable environment. However, the current experiment could not assess causation. It is possible that a bidirectional relationship exists between EF variations and SEV deviations. Future studies can investigate whether stress exposure at baseline predicts SEV deviation and EF performance in the future. Additionally, recovery from stress-related functional network alterations has been observed after stress removal.[67] As increased plasticity during development presents substantial potential for change,[64] alterations in SEV development and their behavioral implications will likely vary as adolescents continue to be exposed to new experiences.

This study provides a new perspective on how SEV changes with age and supports EF, but several limitations should be considered. Here, higher SEV predicted better EF during development. While not observed in this study, SEV may become too excessive to be beneficial. Additional work is needed to investigate this possibility in populations not considered here. For instance, future research can explore whether individuals with attention-deficit/hyperactive disorder would show higher SEV than their peers and if this elevated variability may be linked to impulsivity. Additionally, since we only had access to EF data in PNC and HBN, we examined the relationship between EF and SEV cross-sectionally. Thus, whether SEV changes during development to support improvement in EF remains inconclusive (but see preliminary analysis in STAR Methods). Answering this question may become possible in the future as well-powered, longitudinal datasets become available.

When investigating the relationship between behaviors and SEV, the fixation and high-cognition brain states may be particularly relevant to consider. Both brain states involve the DMN, which has been implicated in a range of cognitive processes spanning from rest to task.[68] Given the large range of behaviors DMN supports, both SEVs' relevance should be carefully considered in different contexts and disorders. Additionally, as fixation SEV appeared to take the longest to reach stabilization, this brain state may be particularly vulnerable to risk exposure and may serve as a potential target for interventions.

Previous literature has examined other forms of neural variability, including variation in BOLD signal over time,[12,69] transitions between different brain states,[19] similarity in functional connectivity between rest and task,[70] and brain state engagement across task trials.[71] As a neural variability measure, SEV differs from previous metrics in important ways. It evaluates variation in the continuous engagement of a given brain state. Our framework allows brain states to overlap temporally, presenting the opportunity to assess each brain state individually. This flexibility allowed us to note variations in developmental trajectory across brain states, which are new findings not gleaned from examining transitions between discrete brain states. Using this approach, future studies can further investigate whether SEV extracted from a brain state specific to a particular cognitive process of interest may have more relevance for EF performance.

Here, we computed SEV using standard deviation since it is the easiest neural variability metric to use.[3,21,69] As other neural variability measures often require users to specify various parameters, they can be more complicated to employ and interpret. But it is important to acknowledge here that since various neural variability measures are computed differently, they likely reveal different information about brain state engagement and can influence result interpretation. As a supplementary analysis, we explored whether a different neural variability measure, entropy, would present complementary understandings (see STAR Methods). Entropy measures how complex or predictable brain signals are over time.[3] Interestingly, we found that brain state engagement also became more complex during development (see STAR Methods). Both SEV and entropy demonstrated increased neural variability in brain state engagement during development. While findings from SEV and entropy align with each other, comprehensively testing whether different neural variability metrics return different behavioral insights requires dedicated experimental testing and remains an ongoing research direction.

In summary, we leveraged a multivariate computational framework to provide novel evidence on variability in continuous brain state engagement during typical development. Across four independent datasets, we established a reliable developmental trajectory for SEV measured during rest, movie, and cognitive control tasks. Its developmental trajectory followed the sensorimotor-to-association-cortex developmental axis and demonstrated sex differences. We additionally presented evidence on SEV's behavioral relevance. Notably, greater alterations from typical SEV development were linked to lower EF performance at that time. These findings present a new account on neural variability's changes and its relevance for EF during typical development.

RESOURCE AVAILABILITY

Lead contact

Requests for further information should be directed to the lead contact, Jean Ye (jean.ye@yale.edu).

Materials availability

This study did not generate new, unique reagents.

Data and code availability

All datasets used in this study are listed in the key resources table. The HCP (https://www.humanconnectome.org/), PNC (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v3.p2), and HBN (https://data.healthybrainnetwork.org/main.php) datasets are publicly available. Original analysis codes have been uploaded to GitHub (https://github.com/jeansye/state_engagement_variability/). Additional data supporting the findings of this study are available from the lead contact author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization, J.Y. and D.S.; supervision, D.S.; visualization, J.Y. and D. S.; methodology, J.Y., W.D., and D.S.; data curation, J.Y., L.T., L.M.C., J.E. H., M.M.H., S.L., S.W.Y., T.B., G.J.B., A.L.W.B., R.B., S.D., H.F., P.G., A.G., A.H., J.-L.M., M.-L.P.M., E.A., F.N., D.P.O., L.P., S.H., N.H., C.B., M.N.S., N. V., H.W., R.W., G.S., H.G., B.C., IMAGEN Consortium, and D.S.; formal analysis, J.Y. and D.S.; writing – original draft, J.Y. and D.S.; writing – results interpretation, J.Y., D.G.G., A.B.-S., B.J.C., and D.S. All authors reviewed the final manuscript.

DECLARATION OF INTERESTS

T.B. served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, and Shire. He received conference support or speaker's fees from Lily, Medice, Novartis, and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. This work is unrelated to the above grants and relationships. G.J.B. has received honoraria from General Electric Healthcare for teaching scanner programming courses. L.P. served in an advisory or consultancy role for Roche and Viforpharm and received a speaker's fee from Shire. She received royalties from Hogrefe, Kohlhammer, and Schattauer. This work is unrelated to the above grants and relationships.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Human Connectome Project (HCP)	Van Essen et al.[40]	https://www.humanconnectome.org/
Philadelphia Neurodevelopmental Cohort (PNC)	Satterthwaite et al.[34]	https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607.v3.p2
Healthy Brain Network (HBN)	Alexander et al.[35]	https://data.healthybrainnetwork.org/main.php
IMAGEN	Schumann et al.[36] and Castellanos-Ryan et al.[37]	https://www.imagen-project.org/
Michigan Longitudinal Study	Cope et al.[38] and Heitzeg et al.[39]	N/A
Queensland Twin Adolescent Brain (QTAB)	Strike et al.[72]	https://openneuro.org/datasets/ds004146/versions/1.0.0
Software and algorithms		
MATLAB	MathWorks	https://www.mathworks.com/
R	The R Foundation	https://www.r-project.org/
SPM	Wellcome Trust Centre for Neuroimaging (UCL)	https://www.fil.ion.ucl.ac.uk/spm/
BioImage Suite	BioImage Suite	https://bioimagesuiteweb.github.io/webapp/
Nonlinear manifold learning to identify brain states	Gao et al.[41]	https://github.com/carricky/2sDM
Original code to compute state engagement variability	Ye et al.[32]	https://github.com/jeansye/state_engagement_variability

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Datasets

This study analyzed two cross-sectional (PNC and HBN) and two longitudinal (MLS and IMAGEN) neurodevelopmental datasets. PNC releases 1–2 and HBN releases 1–10 were included. Informed consent was obtained from all participants and/or their parent or guardian. Study procedures were approved by the corresponding ethics committee in each dataset. We first studied SEV developmental trajectory in two publicly available cross-sectional datasets. Given the caveats of using cross-sectional datasets to study developmental trajectories, we validated our results in two longitudinal datasets we had access to. Importantly, both longitudinal datasets recruited slightly older participants than the two cross-sectional datasets. These two longitudinal datasets allowed us to investigate whether we would observe an age-by-sex interaction effect on SEV and if SEV would continue to change in a consistent pattern in later adolescence and early adulthood.

Since two resting-state runs were available from HBN, we selected the one with the lower mean framewise displacement (MFD). Only the first Go/No-Go run from MLS was analyzed here to retain as many visits as possible while keeping the run number consistent across participants. For the IMAGEN cohort, we only included participants with all three visits and used all of their available Stop Signal data. No additional selection was performed for PNC rest and HBN *Despicable Me* movie data (only one run of data was collected).

fMRI data preprocessing and exclusion

The acquisition parameters for PNC, HBN, MLS, and IMAGEN have been detailed elsewhere.[34,36–39,42] We applied standard preprocessing procedures described in previous work to the structural and functional data from all datasets.[73] Structural data was nonlinearly registered to the standard MNI-152 space. We then performed slice time (in PNC and MLS only) and motion correction on the fMRI data using SPM8 before linearly aligning it to the structural data. Additional data cleaning was carried out in BioImage Suite. This included the regression of covariates of no interest, including linear and quadratic drift, a 24-parameter model of motion, and mean white matter, cerebrospinal fluid, and gray matter signals. We additionally temporally smoothed (cutoff frequency approximately at 0.12Hz) and extracted time series data using the Shen-268 atlas.

Different motion thresholds were adapted to mitigate artifacts across paradigms. Since prior work described scrubbing as an effective way to limit motion effects,[74] time points with over 0.45 framewise displacement were censored for resting-state analysis. Participants with over 20% of their time points scrubbed due to motion were excluded from further analysis. For the HBN movie, MLS Go/No-Go, and IMAGEN Stop Signal fMRI data, we avoided scrubbing to preserve the continuous nature of the paradigms. Individuals with MFD over 0.25 were excluded from the HBN movie and IMAGEN Stop Signal cohorts. Participants with MFD over 0.2 were removed from the MLS Go/NoGo cohort.

The MFD used for exclusion varied slightly here since the current study performed secondary analysis on multiple curated large-scale datasets, and we only had access to partly preprocessed MLS data. Our in-house pipeline computed framewise displacement similar to what Satterthwaite and colleagues[75] described. Whereas the MLS dataset was preprocessed using methods from Power and colleagues.[74,76] As Yan and colleagues[77] have shown, framewise displacement values computed using different methods are highly correlated, but often show a slight variation in offset. As the same number extracted using different methods would not be exactly equivalent, we attempted to match framewise displacement values generated using different methods. While not being able to use the exact same motion cutoff across datasets may be a limitation of working with curated datasets, obtaining the same developmental trajectory with data preprocessed using slightly different pipelines demonstrated the reliability of our results. Additionally, in a sensitivity analysis, we reran our models while including motion and obtained the same results as reported in the main text (see "Sensitivity analysis: motion and intracranial volume").

We applied additional exclusion criteria in each dataset. For the PNC rest cohort, we retained 1325 participants after excluding individuals failing preprocessing benchmarks (i.e., missing resting-state fMRI data, issues with skull stripping, nonlinear or linear registration). All participants had 124 volumes. We removed individuals if they were missing brain coverage (N = 27), had over 20% of their volumes scrubbed due to motion (N = 72), or were missing age information (N = 17). To ensure that no one time point showed a significantly worse fit than the others during non-negative least-squares regression, we removed participants if any of their time points showed a significant outlier residual (N = 1).

For the HBN rest cohort, 1588 participants remained after excluding individuals who did not pass preprocessing benchmarks or had missing resting-state data. We also removed individuals with an incomplete scan (fewer than 375 volumes; N = 48). Similar to the PNC rest cohort, individuals with missing brain coverage (N = 148), over 20% of their volumes scrubbed due to motion (N = 38), and missing age information (N = 79) were excluded from further analysis. No participant showed a significant outlier residual in the model.

For the HBN movie cohort, we had 1718 participants after excluding people who did not meet preprocessing benchmarks. To preserve the continuous nature of the naturalistic paradigm, we did not censor volumes based on motion here. Instead, individuals with mean framewise displacement (MFD) over 0.25mm were excluded (N = 195). We additionally removed participants with an incomplete scan (fewer than 750 volumes; N = 49), missing brain nodes (N = 80), or behavioral information (N = 82). No participant in this cohort had any outlier residual.

Preprocessing for the MLS longitudinal data was performed slightly differently. Exclusion criteria were first applied to each visit. We retained 493 cohort 1 visits and 669 cohort 2 visits after selecting ones that passed all preprocessing benchmarks and had an MFD less than 0.2mm for the first Go/No-Go task run. Each task run had 93 volumes. To retain as many visits as possible for longitudinal analysis, we removed brain nodes with incomplete coverage from all participants (instead of runs with missing brain coverage; 16 and 18 brain nodes were removed from cohorts 1 and 2, respectively). Four visits from cohort 2 were excluded due to having an outlier residual during regression. The last exclusion criteria removed participants with only 1 available visit (final N: cohort 1: 479 visits, 103 unique participants; cohort 2: 639 visits, 150 unique participants).

For the IMAGEN dataset, we only analyzed participants with all three visits available. After preprocessing exclusion criteria were applied, we retained 660 participants. We excluded individuals if their visits showed MFD over 0.25 (N = 116). Almost all participants had the same number of volumes from visit 1 (444 volumes). The volume number varied in visit 2 (most participants had between 300 to 500 volumes) and 3 (most participants had between 300 to 370 volumes). For this reason, we decided to exclude anyone if they had fewer than 444 volumes for visit 1 (N = 2) or fewer than 300 volumes for visit 2 and 3 (N = 2). We additionally excluded participants with missing brain coverage (N = 4) or outlier residuals (N = 6).

After these exclusion criteria, 1208 PNC participants (female: 658; age: 14.688 ± 3.321; age range: 8-21), 1275 HBN resting-state participants (female: 491; age: 11.693 ± 3.39; age range: 5.96-22.07), 1312 HBN movie participants (female: 505, age: 11.361 ± 3.606; age range: 5.13-22.07), 103 MLS cohort 1 participants (female: 40; ages 7.6-21.7 years), 150 MLS cohort 2 participants (female: 56; 16.1-28.5 years), and 530 IMAGEN participants (female: 319; data collected at 14, 19 and 23 years old) were included in our analyses.

Race information was additionally available from both the PNC and HBN datasets. In our PNC analysis, 518 participants identified as Black or African American; 2 as Native American, American Indian or Alaska Native; 562 as European American; 99 identified with more than one race; and 23 identified with others. Four PNC participants were missing race information. For our HBN rest analysis, 159 participants identified as Black or African American; 642 as White or Caucasian; 105 as Hispanic; 40 as Asian; 8 as Indian; 1 as American Indian or Alaskan Native; 2 as Native Hawaiian or other Pacific Islander; 205 identified with more than one race; 18 identified with others; 3 people reported unknown; and 13 participants chose to not specify. Race information was missing from 79 HBN rest participants. For our HBN movie analysis, 167 participants identified as Black or African American; 652 as White or Caucasian; 114 as Hispanic; 42 as Asian; 8 as Indian; 1 as American Indian or Alaskan Native; 1 as Native Hawaiian or Other

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Pacific islander; 219 identified with more than one race; 21 identified with others; 6 participants reported unknown; and 12 participants chose to not specify. Race information was missing from 69 HBN movie participants. In our sensitivity analysis, we found that age's effect on SEV remained consistent when covariates including race were included in the models (see "Sensitivity analysis: other covariates").

METHOD DETAILS

Brain states information

We replicated our prior work here to identify recurring brain states.[41] In brief, we applied nonlinear manifold learning and 2-step Diffusion Mapping to project task-based fMRI data from the Human Connectome Project S500 release[40] into a low-dimensional space. Data from the minimal HCP preprocessing pipeline was used here. We included six tasks (motor, working memory, social, emotional, relational, and gambling) from 390 participants for brain state identification after quality control.[41] Identifying brain states in the HCP dataset presented an opportunity to extract brain states covering low- (e.g., motor movement) to high-level (e.g., working memory and emotion processing) cognitive processes. Secondly, by applying brain states identified in the HCP to other independent developmental datasets, we mitigated the concerns of circular analysis.

After fMRI data was reduced and projected into a lower-dimensional space, time points showing similar activation patterns were closer together. K-means clustering was then used to identify 4 recurring brain states with distinct activation patterns. The number of brain states was determined using the Calinski-Harabasz criterion.[78] A range of potential state numbers were explored, with four showing the largest Calinski-Harabasz value (i.e., the ratio between within- and between-cluster dispersion). Based on the dominant task conditions in each brain state (Table S3), we characterized them as fixation, high-cognition, low-cognition, and cue/transition. The centroid of each state cluster served as its representative time point for later analyses.

For reproducibility, prior work[41] have tested different parameters and replicated brain states in an external sample, the UCLA Consortium for Neuropsychiatric Phenomics dataset.[79] We have also examined what brain networks were activated and deactivated to provide additional support for their validity. For each representative time point, we first identified the activated and deactivated brain regions in a set of canonical brain networks (defined as having activation above or below 0, respectively). The activation or deactivation percentage was computed by dividing the number of activated or deactivated brain regions by the total number of brain regions in a network.

We found that different brain networks were engaged in each brain state. When looking at the three networks showing the highest activation percentages for each brain state, we found that the fixation brain state recruited the default mode network (DMN; 88.89%), the motor network (85.71%), and the medial frontal network (MFN; 82.76%); the high-cognition brain state recruited the visual association network (VAs; 100%), the visual II network (88.87%), and the frontoparietal network (FPN; 82.35%); the low-cognition brain state recruited the motor network (100%), the MFN (86.21%), and the cerebellum (84%); the cue/transition brain state recruited the visual I network (100%), the VAs network (72.22%), and the visual II network (66.67%).

When looking at the three networks showing the highest deactivation percentages for each brain state, we found that the fixation brain state showed deactivation in visual networks (the VAs network: 94.44%; the visual I network: 66.67%; the visual II network: 66.67%); the high-cognition brain state showed deactivation in the motor network (87.76%), the DMN (83.33%), and the subcortical network (79.31%); the low-cognition brain state showed deactivation in visual networks (the visual I network: 100%; the visual II network: 66.67%; the VAs network: 66.67%) as well as the DMN (66.67%); and the cue/transition brain state showed deactivation in the MFN (89.66%), the DMN (88.76%), and the motor network (86.37%).

The activation of different brain networks followed what cognitive processes were associated with each state (Table S3). For example, the entire motor network was activated for the low-cognition state, which was strongly associated with the motor task. The fixation brain state, which consisted of the fixation time points from different tasks, involved activation in the DMN and deactivation of the FPN. The high-cognition brain state, which included time points from task conditions with higher cognitive loads, showed FPN activation.

State engagement variability

State engagement variability was then evaluated using a recently introduced framework[32] (Figure 1), which allows brain states to overlap spatially and temporally to provide a continuous, moment-to-moment measure of brain state engagement. This approach extended the recurring brain states identified earlier to PNC, HBN, MLS, and IMAGEN using non-negative least-squares regression. Specifically, each brain state's representative time point was regressed from each time point of interest from the four datasets. This step returned a beta coefficient for each state at each time point, indicating its engagement at that moment. Continuous assessment allowed us to examine variability in engagement for each brain state separately. State engagement variability was operationalized as the standard deviation of each state's beta coefficients over time. We used this approach to extract state engagement variability, our brain measure of interest, from all datasets analyzed here.

Peak age identification in MLS

We combined both MLS cohorts together to visualize the longitudinal trajectory and explore potential sex differences. For consistency, we re-extracted SEV after removing the same set of brain nodes with missing coverage (N = 19) from both cohorts.

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Additionally, one cohort 1 and four cohort 2 participants were excluded due to having outlier residuals. The final analysis for identifying peak age included 1116 visits and 252 unique participants.

To investigate whether female participants reached stabilization before male participants, we fit a linear mixed-effects model to examine the segmented relationship between SEV and age, adjusting for sex. The segmented linear mixed-effects model is expressed with the following piecewise formula:[80] $y_{ij} = \beta_0 + \beta_1 Sex_i + \beta_2 Age_j + \beta_3(Sex_i \cdot Age_j) + \beta_4(Age_j - \psi)\, I(Age_j > \psi) + u_{0i} + \epsilon_{ij}$ where $\beta_4(Age_j - \psi)\, I(Age_j > \psi)$ indicates the change in the slope of age at scan after the break point, applied only when age is above the change point. We implemented this model using lme4 and segmented.lme in R. We set the number of change points to 1 and the initial break point to 18 before the model iterated and estimated the change point for female and male participants separately. The model allows for random effects in each parameter, including the break point and the slope-difference parameters. We assume independent random effects for each model parameter, with all others set to their default values.

Behavioral analysis in PNC and HBN

To understand the behavioral implications of SEV changes across development, we studied its association with EF. For PNC, CNB tasks focusing on complex cognition (Penn Verbal Reasoning Test, Penn Matrix Reasoning Test, and Penn Line Orientation Test) and executive control (Penn Conditional Exclusion Test, Penn Continuous Performance Test, and Penn Letter N-back Test) were analyzed. An efficiency score was computed for each task based on previous literature.[81] Specifically, response and accuracy scores were first standardized across participants. We then multiplied the response score by -1 before summing it with the accuracy score. For HBN, the standardized scores from the Card Sort, Flanker, List Sorting Working Memory, and Pattern Comparison Processing Speed paradigms were used. After removing individuals with missing behavioral data, 1161 PNC, 1189 HBN rest, and 1229 HBN movie participants were included in the EF and state engagement variability analysis.

Exploratory analysis: how SEV related to EF

To further explore the link between SEV and EF, we performed mediation analysis to explore if SEV mediated the relationship between age and EF in PNC, HBN rest, and HBN movie cohorts. Since all SEVs demonstrated a significant association with age (Figure 2), We opted to extract an overall SEV using PCA for mediation analysis to limit the number of tests performed. The 1st SEV PCA component accounted for 92.786%, 91.567%, and 94.212% of the variance for PNC rest, HBN rest, and HBN movie, respectively. Pearson correlations were performed between variables before they were entered in a mediation model. EF scores increased with age (PNC: $r = 0.498$, $p < 0.001$; HBN rest: $r = 0.631$, $p < 0.001$; HBN movie: $r = 0.685$, $p < 0.001$). Overall SEV positively correlated with EF when controlling for age (PNC: $r = 0.089$, $p = 0.002$; HBN rest: $r = 0.071$, $p = 0.015$; HBN movie: $r = 0.12$, $p < 0.001$).

We found that SEV partially mediated the relationship between age and EF in all three cohorts (Figure S2; Table S4). However, an important limitation to note here is that this analysis was performed in cross-sectional datasets. Thus, it remains unclear whether changes in SEV support improvement in EF during development. To further investigate this possibility, we performed preliminary analyses in the Queensland Twin Adolescent Brain (QTAB) dataset.[72] Two neuroimaging and behavioral time points were collected from each QTAB participant. After preprocessing and quality control, 281 participants were included in the final analysis (age during visit 1: 11.344 ± 1.316; age during visit 2: 13.026 ± 1.505). In QTAB, data from several NIH Toolbox subscales, including Flanker, Card Sorting, and Pattern Comparison Processing Speed, were available from both visits. Thus, similar to our main analysis, we used PCA to assess overall EF and SEV. We then took the difference between visits to study whether SEV changes correlated with EF improvement during development. Our results showed a positive effect size between the two ($r = 0.079$, $p = 0.188$). While this result was not significant, it is important to note that a much larger sample size is required to detect the association we hoped to examine (16 times larger than needed to find a main effect[82]). QTAB has a relatively small sample size and only two time points. It is very possible that we simply do not have the power to study our question of interest in QTAB. However, these results are promising as a first attempt. Testing this question formally in a well-powered study remains an exciting future direction as well-powered longitudinal data become available.

Sensitivity analysis: motion and intracranial volume

Various methods were employed to account for motion across the four datasets. Consistent results were observed regardless of how we identified individuals with excessive motion (i.e., scrubbing or excluding based on MFD over the entire scan). While these findings suggested the trajectory we observed was unlikely to be driven by motion, we reran our analysis while including MFD as a covariate. This analysis was performed in datasets where motion threshold was based on MFD, as no volume with excessive motion was scrubbed. Additionally, to examine whether age's effect on SEV was robust to anatomical changes across development, we extracted and included intracranial volume (ICV) from each participant as a covariate. This was done in all datasets but IMAGEN since we unfortunately did not have access to anatomical data needed to extract ICV from this dataset. We successfully replicated results reported in the main text when controlling for motion and ICV.

In the PNC rest dataset, SEV increased with age when controlling for ICV (MANOVA; age: $F(4,1200) = 21.039$, $p < 0.001$; ICV: $F(4,1200) = 8.359$, $p < 0.001$; sex: $F(4,1200) = 1.140$, $p = 0.336$; age-by-sex: $F(4,1200) = 3.098$, $p = 0.015$). In the HBN rest dataset, age also showed a significant effect on SEV when controlling for ICV (MANOVA; age: $F(4,1267) = 36.541$, $p < 0.001$; ICV: $F(4,1267) = 10.163$, $p < 0.001$; sex: $F(4,1267) = 1.90$, $p = 0.107$; age-by-sex: $F(4,1267) = 0.566$, $p = 0.687$). In HBN movie, we still observed a significant main age effect on SEV after controlling for motion and ICV (MANOVA; age: $F(4,1303) = 61.427$,

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$p < 0.001$; motion: $F(4,1303) = 36.481$, $p < 0.001$; ICV: $F(4,1303) = 19.125$, $p < 0.001$; sex: $F(4,1303) = 4.329$, $p = 0.002$; age-by-sex: $F(4,1303) = 0.491$, $p = 0.742$).

We further replicated our results in MLS after controlling for motion and ICV. In the younger MLS cohort 1, SEV increased with age across three of the brain states when controlling for both motion and ICV (Table S5). In the older MLS cohort 2, same as in the main text, age did not show a significant effect on SEV after controlling for MFD and ICV (Table S5).

Finally, in the IMAGEN dataset, fixation SEV collected at age 14 was lower than SEVs collected at ages 19 and 23 when controlling for MFD (Table S5). No significant age effect was observed for the other SEVs (Table S5). Importantly, when controlling for motion, we again found a significant interaction between sex and later visit on SEV across all four brain states (LMEs; fixation: beta = 0.046, $t(1056) = 2.970$, $p = 0.003$; high-cognition: beta = 2.888e-02, $t(1056) = 2.853$, $p = 0.004$; low-cognition: beta = 1.087e-02, $t(1054) = 3.599$, $p < 0.001$; transition: beta = 3.178e-02, $t(1053) = 3.245$, $p = 0.001$; see other covariate results in Table S5). As these findings were consistent with our main text results, it was unlikely that motion and ICV drove the SEV trajectory observed in this study.

Sensitivity analysis: other covariates

As an additional sensitivity analysis, we explored whether we would still observe age-related changes in SEV when we controlled for variables assessing an individual's family and neighborhood environment as well as their mental and physical health. We performed this analysis in the two publicly available datasets. Thus, not the same behavioral data were available to be included in the model for each dataset.

In PNC, age showed a consistent main effect on SEV ($F(4,540) = 6.768$, $p < 0.001$) when controlling for race ($F(20,2172) = 1.186$, $p = 0.256$), medical condition ($F(16,2172) = 1.06$, $p = 0.388$), and self-reported substance use ($F(4,540) = 0.473$, $p = 0.756$). For HBN rest, age again showed a significant main effect on SEV ($F(4,899) = 31.907$, $p < 0.001$) when race ($F(40,3608) = 0.819$, $p = 0.784$), family annual income ($F(48,3608) = 1.075$, $p = 0.336$), and self-reported neighborhood safety ($F(4,899) = 4.127$, $p = 0.003$) were included in the model. We again replicated this result using SEV extracted from the HBN movie dataset (age: $F(4,892) = 37.340$, $p < 0.001$; race: $F(36,3580) = 1.056$, $p = 0.378$; family annual income: $F(48,3580) = 1.174$, $p = 0.193$; self-reported neighborhood safety: $F(4,892) = 0.288$, $p = 0.886$). Altogether, SEV demonstrated consistent age-related changes when controlling for these additional covariates.

Brain states from a developmental population

In our main text, we constructed recurring brain states in the HCP dataset, which mainly recruited young adult participants. Thus, it is unclear whether our observed results simply reflect adolescents' brain states becoming more and more adultlike instead of intrinsic neural flexibility increasing with age. To provide further support for the latter interpretation, we investigated if the same developmental trajectory may be observed for SEV extracted using brain states from a developmental population.

We turned to the HBN movie dataset to derive brain states in a developmental population. This dataset was chosen since participants were presented with the same stimuli over time. Further, naturalistic stimuli such as movies may allow us to identify brain states involved in various processes. We leveraged fMRI data from both movie runs (*Despicable Me* and *The Present*; 1000 TRs in total) from 1286 HBN participants. Following our previous work, we applied nonlinear manifold learning to extract brain states in this dataset. We identified four recurring brain states in this dataset using K-means clustering, with the number of brain states again determined by the Calinski-Harabasz criterion.[78] Notably, all HBN brain states showed significant correlations with HCP brain states (Table S6). We avoided applying HBN brain states to HBN participants to prevent circular analysis. But we repeated our age-related analysis in PNC, MLS, and IMAGEN.

While we did not observe a significant association between age and HBN-derived SEVs in PNC (MANCOVA; age: $F(4,1201) = 1.713$, $p = 0.145$; sex: $F(4,1201) = 3.897$, $p = 0.004$; age-by-sex interaction: $F(4,1201) = 0.615$, $p = 0.652$), we were able to obtain results consistent with the main text findings in both longitudinal datasets.

In the younger MLS cohort 1, HBN state 1 SEV increased with age. Notably, we found a significant age-by-sex interaction effect on SEV for all HBN brain states (Figure S3A; Table S7). Similar to what we presented in the main text, these findings suggest changes in SEV over development differed by sex, with female participants potentially stabilizing before male participants (Figure S3A). No significant age, sex, or age-by-sex interaction effect was observed in MLS cohort 2 (Table S7). The pattern of weaker associations between HBN-derived SEVs and age in the older MLS sample aligned with what we reported in the main text using HCP brain states.

We further replicated our results in IMAGEN using HBN-derived brain states. HBN SEVs collected at ages 19 and 23 were greater than those collected at age 14 (Table S7; Figure S3B). Same as in our main text, no significant difference was found between ages 19 and 23 SEVs (Table S7). Notably, we found a significant interaction between sex and later visit on SEV across all four HBN brain states (Table S7). All of these results were the same as what we presented in the main text using HCP brain states. We replicated our findings in MLS and IMAGEN using brain states extracted from a developmental population. These results suggest longitudinal datasets may present increased power in building our understanding of how brain dynamics change over development. Notably, MLS and IMAGEN included participants older than those in the HBN dataset. Yet, we observed SEV increasing with age in participants from both longitudinal datasets using brain states identified in a younger sample. These findings strongly suggest that SEV's developmental trajectory reflects intrinsic neural flexibility increasing with age instead of individuals' brain states becoming more adult-like.

Control analysis: intrinsic brain state engagement

Previous literature has noted intrinsic brain activity changing with age.[29] Thus, we explored if intrinsic brain state engagement also changed with age. To examine brain state engagement, we computed relative state engagement (RSE) for each brain state (i.e., the sum of each state's engagement divided by the sum of all brain state engagement). As RSEs from all brain states added up to 1, we performed an ANOVA analysis separately for each brain state's RSE to study age effect. We additionally focused on resting-state fMRI data here. Unlike SEV, RSE across the four brain states did not consistently correlate with age over development. In the PNC rest cohort, there was no significant age effect on fixation ($F(1,1271) = 0.154$, $p = 0.695$) or transition RSE ($F(1,1271) = 0.006$, $p = 0.940$). But older PNC participants engaged the high-cognition brain state more ($F(1,1271) = 9.829$, $p = 0.003$) while recruiting the low-cognition brain state less ($F(1,1271) = 6.682$, $p = 0.010$). However, this pattern was not replicated in the HBN rest cohort, where age did not show a significant main effect on RSE (fixation: $F(1,1204) < 0.001$, $p = 0.984$; high-cognition: $F(1,1204) = 1.201$, $p = 0.273$; low-cognition: $F(1,1204) = 2.592$, $p = 0.108$); transition: $F(1,1204) = 0.586$, $p = 0.444$). The lack of consistent changes in brain state engagement with age indicated that SEV developmental trajectory was unlikely to be driven by changes in brain state engagement across development.

Exploring a different neural variability metric

In this study, we computed SEV using standard deviation since it is the simplest form of neural variability.[3,21] However, there are many different ways to assess variability in brain signals. For instance, entropy can be used to evaluate the predictability and complexity of brain signals. Since it is not an exact equivalent to variance measures such as standard deviation, entropy may reveal different information.[3] To investigate whether entropy in brain state engagement also changes in a similar manner as SEV, we extracted entropy from all four datasets and investigated its relationship with age. Specifically, we computed sample entropy[83] using parameters described in previous work[11] ($m = 2$, $r = 0.5$).

Age effect was not significant in PNC (MANCOVA; $F(4,1201) = 2.272$, $p = 0.060$). But consistent with our SEV results, a significant main age effect was found in HBN rest (Figure S4A) and movie datasets (Figure S4B). We also obtained results consistent with our SEV findings in IMAGEN. Participants showed lower fixation, high-cognition, and transition entropy at age 14 compared to ages 19 and 23 (Table S8; Figure S4C). Same as SEV, entropy at ages 19 and 23 did not differ significantly (Table S8). Interestingly, we did not find a significant age effect on entropy in MLS cohort 1 (Table S8) or cohort 2 (Table S8). In HBN rest, HBN movie, and IMAGEN, higher entropy was found in older participants (Figure S4). For the entropy measure we used, a higher value indicated more complex brain signals. Thus, the entropy results we showed here aligned with the SEV findings reported in the main text.

QUANTIFICATION AND STATISTICAL ANALYSIS

MANOVA investigated main age, sex, and age-by-sex interaction in PNC and HBN, whereas linear mixed-effects model was used to examine age effect in the longitudinal MLS and IMAGEN datasets. We included age and sex as fixed effects and participants as random effects. FDR correction was performed on all primary analyses with $q < 0.05$ considered as significant. We checked that SEV values followed a normal distribution before performing analyses. Brain states and SEV were extracted using MATLAB. MANOVAs and LMEs were conducted in R.

EF and age predictions were performed using external validation. To predict EF and age using SEVs, we first trained a linear model in one dataset before testing the prediction model in an independent dataset. Prediction accuracy was estimated by computing the correlation between predicted and observed behaviors. We successfully predicted EF when model was trained in PNC (model parameters: fixation: 1.628; high-cognition: 2.671; low-cognition: 6.675; cue/transition: -4.231) or HBN (model parameters: fixation: -20.203; high-cognition: 83.631; low-cognition: -5.087; cue/transition: 6.951). Age can also be predicted using SEV from PNC (model parameters: fixation: 0.518; high-cognition: 10.112; low-cognition: 8.032; cue/transition: -8.733) or HBN (model parameters: fixation: 0.412; high-cognition: 11.027; low-cognition: 3.679; cue/transition: -2.780).