Functional Connectivity Uniqueness and Variability? A Signature of Cognitive and Psychiatric Problems in Children

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Article

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Abstract

Brain functional connectivity (FC) derived from functional magnetic resonance imaging (fMRI) has been serving as a potential “fingerprint” for adults. However, intra-subject variation of FC can be substantial and carry biologically meaningful information, especially during adolescence, a time of intense brain changes. Here, for the first time, we performed a large-scale analysis on cross-scan FC stability and its association with a diverse range of health measures in children from the Adolescent Brain Cognitive Development (ABCD) data. Functional network connectivity (FNC), a network analog of FC, was extracted via an automated independent component analysis framework on 9071 subjects (age: 9~11 years) and compared across 4 scans. We found that the FNC profile can identify a given child from a large group with high accuracy (> 80%), though intra-subject variations exist cross-scan. The robustness of this finding is verified by replicating the child identification using the second-year scans and between longitudinal scans with a two-year interval. Moreover, cross-scan FNC stability was predictive of sleep condition, cognitive performance, and psychiatric problems in children, with higher stability correlated with better cognitive performance, longer sleep duration, and less psychotic expression. Meanwhile, parental psychopathology and prenatal exposure were associated with the FNC stability in their children. Overall, our findings show that a child’s connectivity profile is not only intrinsic but also exhibits reliable variability cross-scan, regardless of brain growth and development. The intra-subject connectivity stability may serve as a valuable biomarker to draw inferences on early cognitive and psychiatric behaviors in children.

Introduction

Functional connectivity (FC) derived from functional magnetic resonance imaging (fMRI) data has shifted neuroimaging focus away from exploring localized brain activity toward characterizing co-activation patterns across distributed brain regions [1,2]. FC has been associated with cognition [3] and various neurological [4] and mental [5,6] disorders. Although the population-based studies have revealed a great deal of knowledge on the FC organization profile, brain FC is assumed to be unique to individuals, regardless of how the brain is engaged during scanning [7]. FC heterogeneity has long been appreciated in fMRI studies, even within the same population [8–10]. By using a multi-condition fMRI dataset from the Human Connectome Project, studies have shown that FC profile can distinguish adult subjects across scan sessions and even between distinct task conditions [7,11,12], acting as a “fingerprint”. A recent study has captured five different functional clusters in the pulvinar with specific connectivity fingerprints, associating with distinct components of cognition [13]. However, an individual’s FC is not constant but continuously changes with remarkable variations at different scales, adapting to internal and external demands [14–16]. That is to say, besides the intrinsic patterns, FC can also exhibit prominent intra-subject variability, which might underly important biological mechanisms [17]. Many existing works have only examined the FC variation within a single scan [18–20], and an individual’s *cross-scan* FC variability has received relatively little attention from the neuroimaging field. A comprehensive understanding of *cross-scan* FC is necessary for developing robust FC-based biomarkers.

Unlike adults, children show considerable growth and development in the brain [21] and might exhibit more temporal variability in brain FC [22,23]. The temporal variation in resting-state FC declines with aging, especially for those FC involved in frontal-parietal and occipital networks [22]. Age is negatively associated with the variability of dynamic brain connectivity states captured by a clustering strategy on dynamic FC estimates [23]. The prominent variation in youths' FC might be due to more neuroplasticity in the adolescent's brain [24,25] or be induced by larger motion artifacts [26] of the adolescent subjects, though this is still far from understood. On the other hand, some other studies assume that FC is unique to an adolescent and show that FC profile can successfully identify an adolescent from a group of subjects [25,27].

Despite such progress, we argue that the exploration of *cross-scan* FC in youths has been limited, as most studies have used relatively small numbers of participants (e.g., sample size < 1000). In addition, many prior studies failed to examine the robustness of FC results across multiple scans and between longitudinal sessions. More importantly, existing work has only focused on the fingerprint property of FC across scans, ignoring the intra-subject FC variation *cross-scan* and its potential relationship with individual behavior in children. The stability of FC across scans can carry meaningfully biological mechanisms, reflected by its relevance to adolescents' neurocognitive development, adverse mental problem outcomes, and other healthy backgrounds. Therefore, there is the need for a reliable large-scale study as the present one that can include more than 9000 subjects with multiple scans collected from longitudinal sessions to comprehensively examine the relevance of the *cross-scan* FC stability to individual differences in behavior and mental conditions.

Here, we investigate the *cross-scan* FC stability in children using a multimodal database called Adolescent Brain Cognitive Development (ABCD). The ABCD database includes more than 11,800 subjects, with multiple scans collected from two longitudinal sessions. This dataset has collected a comprehensive range of measures related to mental problems, cognitions, and other health backgrounds [28] that have been shown useful for the investigation of the relationship between adolescent behaviors and brain functions [29]. Our hypothesis is twofold. First, the FC profile of children shows intrinsic patterns across scans, and the intrinsic patterns can identify a given child from a large group of subjects. We also expected this identification would be successful between longitudinal sessions, regardless of the developments and changes in the children's brains. Our second hypothesis is that children's FC also shows intra-subject variations across scans, which will predict distinct behavioral phenotypes in children, such as cognitive performance, psychiatric problems, and sleep conditions.

Results

Flowchart of the *Cross-scan* Functional Connectivity Analysis

Fig. 1 displays the flowchart of the cross-scan functional network connectivity (FNC) analysis. We first applied a Neurmark framework to extract robust intrinsic connectivity networks (ICNs) that are comparable across subjects, scans, and sessions. FNC was estimated using the time-courses (TCs) of ICNs from each scan. After obtaining the FNC matrix of each scan, *cross-scan* FNC similarity was measured by the correlation between FNC from different scans. Then individual identification was performed based on the cross-scan FNC similarity. Finally, we examined the associations between intra-subject FNC similarity and individuals' behaviors via a linear mixed-effect model (LMM).

Functional Networks

53 ICNs were extracted by the Neurromark framework, with activation peaks falling on the majority of cortical and subcortical gray matter areas across the whole brain. The ICNs were assigned to seven different functional domains according to their anatomical locations and functional information [14], including subcortical (SC), auditory (AUD), visual (VS), sensorimotor (SM), cognitive-control (CC), default-mode (DM), and cerebellar (CB) domains. Details of the spatial maps and coordinates of ICNs are provided in the supplementary materials.

Intra-subject FNC Shows High Similarity across Scans

Fig. 2a displays the FNC of subjects with maximum and minimum intra-subject FNC similarities between scans. Children show different levels of cross-scan FNC similarity. For subject INVX2TWFHMP, the FNC of scan 1 and the FNC of scan 2 share the highest intra-subject similarity (r = 0.9448). In contrast, for subject INVZF82Z2N1, the FNC show more variability between scan 1 and scan 2, where the intra-subject FNC similarity is only r = 0.1914. Fig. 2b displays the percentage of children with intra-subject FNC similarity larger than a given percentage of inter-subject FNC similarity, from 60% to 99%. Our results show that intra-subject FNC similarity is larger than a majority of inter-subject FNC similarity, though intra-subject FNC variability exists. The FNC shows the highest intra-subject similarity between scan 1 and scan 2. More than 90% of subjects have intra-subject FNC similarity larger than 60% of inter-subject FNC similarity and more than 65% of subjects have intra-subject FNC similarity larger than 99% of inter-subject FNC similarity. The intra-subject FNC shows the lowest similarity between scan 1 and scan 4. Still, more than 80% of subjects have intra-subject FNC similarity larger than 60% of inter-subject FNC similarity, and about 40% of subjects have intra-subject FNC similarity larger than 99% of inter-subject FNC similarity.

The results are replicated by examining the scans from the second-year session. Similarly, subjects can have different levels of cross-scan FNC similarity. FNC shows the highest intra-subject similarity between scan 1 and scan 2 and the lowest intra-subject similarity between scan 1 and scan 4. FNC also shows intra-subject similarities between longitudinal scans. Although a two-year time interval between scans incurred a significant decrease in intra-subject similarity, the intra-subject similarity is still larger than the majority of inter-subject FNC similarity, especially when the FNC was averaged within the session.

Individual Identification using Whole-brain FNC

Fig. 3 shows the identification results of each pair of identification. At the baseline session, the identification accuracy was 93.99%, 84.78%, 81.87%, and 93.10% based on the database-target of scan 1-scan 2, the target-database of scan 1-scan 3, the target-database of scan 1-scan 4, and the target-database of scan 1-scan mean respectively. The identification was replicated by using the FNC of the second-year scans. Similar to the results from the baseline, the highest identification accuracy 95.16% was achieved based on the database-target of scan 1-scan 2, while the lowest identification accuracy 82.80% was achieved based on the database-target of scan 1-scan 4.

The individual identification was further performed using the FNC of between longitudinal scans. Scans from the baseline session were the database and scans from the second-year session were the target. Although more intra-subject FNC variations were introduced, the FNC of a child from the baseline session can still be used to identify his/her FNC from the second-year follow-up session. The highest accuracy was 91.43%, which was achieved by averaging the FNC across all four scans within each session before identification.

The nonparametric permutation testing shows that the average identification accuracy was 50% if the identity was shuffled for each scan. The real identification accuracy was significantly higher than the accuracy obtained by the permutation tests.

FNC Stability Predicts Cognitive Performance

The cognitive measures were positively correlated with the intra-subject FNC stability (False discovery rate [FDR] corrected, $q < 0.05$). Specifically, 10 out of 10 of the cognitive summary scores were positively correlated with FNC stability, with correlation r values ranging from 0.0376 to 0.1070. The Total Composite Score was the score most significantly positively correlated with the FNC stability ($r = 0.1070$, Cohen's $d = 0.2152$, $p = 4.82\times10^{-24}$). For the neurocognitive battery in the subdomain, TPVT was the score most significantly positively correlated with the FNC stability ($r = 0.0841$, Cohen's $d = 0.1688$, $p = 1.54\times10^{-15}$) while TFT was the score least significantly positively correlated with intra-subject FNC stability ($r = 0.0376$, Cohen's $d = 0.0753$, $p = 3.68\times10^{-4}$). To better visualize the associations, we divided the children into four groups from low cognitive performance to high cognitive performance according to each cognitive score (group 1: 0%~25%, group 2: 25%~50%; group 3: 50%~75%, and group 4: 75%~100%) and the averaged *cross-scan* FNC stability within each group is displayed using bar plots in Fig. 4. Clear increasing trends can be observed along group 1 to group 4, indicating that children with good cognitive performance tended to have higher FNC stability.

FNC Stability Predicts Psychiatric Problems

The psychopathological measures of children were negatively correlated with the intra-subject FNC stability. 12 out of 20 psychiatric problem scores show significantly negative correlations with FNC stability, with r values ranging from -0.0257 to -0.0496 (FDR corrected, $q < 0.05$). The social problem score was the score most significantly negatively correlated with the FNC stability ($r = -0.0496$, Cohen's $d = -0.0992$, $p = 2.38\times10\text{-}6$). Similarly, we divided the children into four groups according to each psychopathological measure. The mean and the standard error of the mean for the *cross-scan* FNC stability of each group were displayed in Fig. 4. The FNC stability show decreasing trends along group 1 to group 4, indicating that children with high psychiatric problem scores tended to have lower FNC stability.

FNC Stability Correlates with Sleep Conditions and Screen Usage

We further found significant associations between FNC stability and the sleep conditions of children. The *cross-scan* FNC stability was negatively correlated with the sleep duration score ($r = -0.0752$, Cohen's $d = -0.1508$, $p = 7.74\times10^{-13}$). In the ABCD measurement system, high sleep duration score indicates short sleep duration (1 = 9-11 hours; 2 = 8-9 hours; 3 = 7-8 hours; 4 = 5-7 hours; 5 = Less than 5 hours). The FNC stability was also negatively correlated with the score that evaluates how long an adolescent falls asleep (sleepdisturb2_p). A higher score in sleepdisturb2_p indicates a longer time to fall asleep. The FNC stability was negatively correlated with other sleep behaviors of adolescents, such as sleepdisturb24_p (evaluates a child feels unable to move when waking up in the morning) and sleepdisturb26_p (evaluates a child falls asleep suddenly in inappropriate situations). Higher scores in these measurements indicate more frequently that the event happens (1 = Never; 2 = Occasionally (once or twice per month or less); 3 = Sometimes (once or twice per week); 4 = Often (3 or 5 times per week); 5 = Always). The overall results indicate that children with worse sleep conditions (e.g., shorter sleep duration or longer time to fall asleep) tended to have lower FNC stability.

Children's screen usage is also negatively correlated with *cross-scan* FNC stability. 14 out of 14 youth screen time utilization scores, including the use of television, internet, cell phone, and video games, show negative correlations with individuals' FNC stability (FDR corrected, $q<0.05$). Children with more screen usage tended to have lower FNC stability. Details of the correlations statistics can be found in the supplementary materials.

FNC Stability Correlates with Parent Psychopathology and Prenatal Exposure

Moreover, parental dimensional psychopathology showed significant correlations with their children's FNC stability (Fig. 5). Specifically, the positive questions in the parents' psychopathology assessment, including asr_q15_p (I am pretty honest), asr_q73_p (I meet my responsibilities to my family), asr_q88_p (I

enjoy being with people), asr_q98_p (I like to help others), asr_q106_p (I try to be fair to others), asr_q123_p (I am a happy person), were positively correlated with the FNC stability of children with r values ranging from 0.0315 to 0.0583 (FDR corrected, $q < 0.05$). In contrast, the negative questions in the parents' psychopathology assessment were negatively correlated with the FNC stability of children with r values ranging from -0.0287 to -0.0482 (FDR corrected, $q < 0.05$). These results indicate that parents with positive behaviors will result in higher FNC stability in children while parents with negative behaviors will result in lower FNC stability in children.

Our analysis also showed that prenatal exposure before and during pregnancy was associated with FNC stability in children. Parents with prenatal exposure to tobacco and marijuana will result in lower FNC stability in children (FDR corrected, $q < 0.05$). Also, a planned pregnancy will result in higher FNC stability in children. The age of the parents during the pregnancy showed significant correlations with FNC stability as well. While older mothers will result in higher FNC stability in children, fathers' ages between 30~40 years old (when the child was born) result in the highest FNC stability in adolescents.

Discussion

The Fingerprint Property of Adolescent's FNC

Brain FC and its network analog, FNC, are believed to provide a window into brain function and intrinsic brain organization [2,40–42]. Neuroimaging studies have successfully established that adults' FC profile shows substantial inter-subject variability, and such variability can distinguish individuals from another scan [7,12]. Unlike adults, children might show more intra-subject variability in FC due to the developments in the brain [43]. More heterogeneous brain states and confounding effects in youths (e.g., head motions) [44,45] might also influence the individual identifications. Recent research has found that the identification of youths is not significantly different from that of adults [25]. However, this study relied on adolescents with a large age range (12~18 years). Brain developments at different ages can be different, potentially introducing unpredictable variability in the identification. Also, the results based on such a small sample size (N = 140) can be biased by the sampling variability, further resulting in replication failures [46]. Our study used large data from the ABCD project with almost the same age to show that the *cross-scan* FNC similarity can be robustly observed in children. We noted that the identification accuracy decreased and the intra-subject FNC variability increased as the time interval of scans increased. These results indicate that the assumption of the FNC uniqueness might oversimplify the interrelationships between brain regions. Accumulated evidence has shown that brain connectivity is highly dynamic with dramatic variations across scans, tasks, and time [47–49]. An individual's FC will show both similarity and variability across scans, depending on the brain state in which the FC is measured [17]. Our result provides the first evidence that single-subject FC will exhibit *cross-scan* variability that might be indicative of brain state during imaging. In other words, as a subject stayed in the scanner for a longer time, their brain state might be far away from the initial "resting-state", resulting in a larger difference between the brain FNC.

We successfully performed the individual identification between longitudinal scans with a two-year interval, although with reduced overall accuracy. This finding is in line with a previous result based on a relatively small sample size, which suggested that a larger time interval can incur a significant decrease in identification accuracy [25]. We further found that averaging FNC across scans within each session can increase the accuracy. Growth and development inside the children's brain will introduce FC variation intra-subject, which is associated with children's neurodevelopment and behaviors [50,51]. Averaging FNC within the same session can mitigate the heterogeneity induced by transient brain states, but not the variability induced by brain development. Our result suggests that the decreased identification accuracy between longitudinal scans can be due to both brain development and the difference in the temporal brain conditions. The successfully longitudinal identification further supports that the FC profile contains fundamental properties that are unique to each child, regardless of the FC developments during adolescence [25].

Individual FNC Stability Predict Adolescent's Behaviors

Besides the intra-subject similarity, children's FNC also showed intra-subject FNC variability across scans. The balance between *cross-scan* FNC similarity and variability does not appear to be driven by random noise but captures physiological and psychological information. The *cross-scan* FNC stability was positively correlated with cognitive performance, including reading recognition, pattern comparison, memory, etc. Previously, neuroimaging studies have been typically focusing on the FC strength and suggesting that its inter-subject variability is relevant to individual differences in behaviors [3,7,52]. However, brain FC is not static, but with considerable variation between tasks and rest, across scans, and even within a single scan [17,49,53]. Spontaneous FC variations can predict the performance of different cognitive tasks [54,55]. Literature also showed that individuals with stable FC across-time show advanced cognitive performance, reflected by the increased accuracy and the more stable response time [56,57]. Our finding has extended the investigation of FC variability within a single scan to the investigation of FC stability across scans and showed robust relationships between *cross-scan* FC stability and cognitions. A possible explanation of this finding is that the resting-state is in a "relaxed" brain condition that ameliorates adaptive reconfiguration of brain networks in the context of cognitive tasks. A stable FC during the execution of cognitive tasks is associated with successful cognition and more difficult task conditions require increased stability of FC [56,57]. The stable FC during the resting-state might facilitate the brain switching from a relaxed condition to a task demand condition that purportedly requires sustained cognition, consequently resulting in better cognitive performance [58].

In addition to the correlations with cognitions, we found negative correlations between FNC stability and the dimensional psychopathology in children. Children with less *cross-scan* FNC stability will have more severe dimensional psychopathological problems and more frequent mania episodes. One interpretation of this finding is that decreased FC stability underlies the dysregulated brain rhythms that characterize psychiatric problems. Of note, increased rumination is associated with higher medial prefrontal cortex to

insula FC variability, suggesting that the intra-subject FC heterogeneity might trigger rumination by enhancing sensitivity to self-referential information [59]. It is also suggested that the unstable FC may be associated with deficits in executive functioning and reflect weaknesses in brain circuits responsible for cognitive control [60]. A growing body of literature has linked dynamic FC patterns to psychiatric problems. Individuals with autism spectrum disorder have larger FC variability in time, associated with the increase depending on autism symptom severity [61]. By using magnetoencephalography, researchers have shown that schizophrenia patients exhibit more trials-to-trials network topology variability during a 2-back working memory task [62]. Increased FC variability has also been observed in both patients with depressed bipolar disorder and major depressive disorder, who shared overlapping symptoms that typically confound the diagnosis [63]. Our results complement the prior work by showing that an individual's FNC exhibits reliable variability across scans, which might signify underlying biological mechanisms in mental health. The stability of *cross-scan* FNC can add information to the connectivity strength and will be a potential brain biomarker that predicts early psychiatric problems in children.

Interestingly, our analysis further showed that the FNC stability of children is also relevant to the parental conditions. The development history of children can be an important indicator of later mental and psychical behaviors in youths [28]. The increase of drug use among pregnant mothers has become a social problem in the US [64]. Prenatal cannabis exposure is associated with a greater risk for psychopathology in adolescents [65]. Here in this study, we found that prenatal tobacco and marijuana exposure is associated with lower *cross-scan* FNC stability during middle childhood. Considering the associations between FNC stability and cognition and dimensional psychopathology, this result underscores the potential to use FNC stability to advance our understanding of the relationships among prenatal drug usage and cognitive developments and mental health among offspring. Another interesting finding of our present study is that the parents' psychopathology was correlated with the FNC stability of children, where the positive behaviors in parents were associated with higher FNC stability in their children while the negative behaviors in parents were associated with lower FNC stability in their children. We speculate that the family environment might influence the stability of FC in children. This speculation is supported by a further analysis showing a positive correlation between children's FNC stability and neighborhood safety, an important living environmental factor. The inherited characteristic can be another cause of these relationships. Analysis including genetic data is needed in future studies for validating this hypothesis.

In sum, our study revealed that children's FNC shows certain similarity and substantial variability across scans from the same day and longitudinal sessions. The intrinsic patterns of FNC successfully identify each child from a large cohort of 9071 subjects. Besides, *cross-scan* FNC stability carries important psychological and physiological information underlying distinct behavioral phenotypes in children. To the best of our knowledge, this is the first attempt to investigate the *cross-scan* FNC on children at a large-scale. Given this foundation, future neuroimaging studies should move beyond the focus of the connectivity uniqueness to an individual, but to investigate the *cross-scan* connectivity variability, probing how intra-subject stability and variability of an individual's functional brain organization provide a window into neuropsychological mechanisms.

Materials And Methods

Participants and behavioral assessments

The present study used a longitudinal dataset shared by the ABCD, the largest long-term study of brain development and child health in the United States (https://abcdstudy.org/). We used the release 2.01 of the ABCD dataset, containing over 11,800 children aged 9-11 years, with two imaging sessions (baseline and the second-year) and multiple scans within each session. The ABCD study incorporated a comprehensive range of measures, including neurocognitive battery, physical and mental health assessments, socioeconomic, ethnic, and other health backgrounds, to assess predictors and outcomes related to different domains [28,29]. The parent's full written informed consent and the child's assent were obtained under protocols approved by the Institutional Review Board. We performed data quality control (QC) on the preprocessed fMRI data via the Neuromark framework [30]. The Neuromark QC yield 9071 subjects for the baseline analysis, 2918 subjects for the second-year analysis, and 2290 subjects for the cross-sessional analysis; each analysis has at least four good resting-state fMRI scans within each session. The basic demographics can be found in Table I.

Table I. Basic Demographics of Subjects

Basic Demographics	**Baseline**	**Second-year**
Total Subject	9071	2918
Age (month)	119.06 ± 7.52	142.86 ± 7.51
Gender (F/M)	4365/4706	1333/1585
Height (inch)	55.28 ± 3.35	60.04 ± 3.53
Weight (lbs)	82.97 ± 23.52	107.57 ± 31.99
Race (W/B/H/A/O)	4771/1325/1863/181/929	1631/317/629/57
Cognition (nihtbx_totalcomp)	86.44 ± 8.99	90.94 ± 7.11
Psychiatric problem (cbcl_scr_syn_totprob)	45.73 ± 11.35	44.78 ± 11.27
Sleep disturbance (sleepdisturb1_p)	1.72 ± 0.81	1.99 ± 0.86

Neuromark Framework

To capture reliable intrinsic connectivity networks (ICNs) and their corresponding TCs for each subject and each scan, a robust independent component analysis (ICA)-based framework called Neuromark [30] was applied to the ABCD data. Unlike atlas-based methods that typically assume fixed brain regions across subjects, the Neuromark can identify brain networks comparable across subjects while adapting single-subject variability with the networks. The effectiveness of Neuromark has been demonstrated in

previous work, with a wide range of brain markers and abnormalities identified in different populations [31–36]. More details of the Neuromark framework are provided in [30] and the supplementary materials.

Functional Network Connectivity

Children's data can be noisy with more confounding effects, such as larger head motions. We therefore performed four additional post-processing steps to carefully regress out the remaining noise in the TCs of ICNs: 1) detrending linear, quadratic, and cubic trends, 2) removal of detected outliers, 3) multiple regression of the head motions parameters (3 rotations and 3 translations) and their derivatives, 4) band-pass filtering with a cutoff frequency of 0.01 Hz-0.15 Hz. Pearson correlation coefficients between post-processed TCs were calculated to measure the FNC for each scan.

FNC Similarity and Subject Identification

We calculated the correlation between whole-brain FNC from different scans to measure the FNC similarity. Specifically, the correlation between FNC of scans from the same subject was defined as the intra-subject FNC similarity while the correlation between FNC of scans from different subjects was defined as the inter-subject FNC similarity. For each subject, there are one intra-subject similarity and 9070 inter-subject similarities. Then we calculated the percentage of children who have intra-subject FNC similarity larger than a given percentage of inter-subject FNC similarities (60%, 70%, 80%, 90%, 95%, and 99%).

We performed individual identification using the FNC similarity. For each subject, we compared his/her intra-subject FNC similarity with a randomly picked inter-subject FNC similarity. The predicted identity was that with the larger correlation value. We performed this step for every subject to obtain an identification vector, which can be used to calculate the overall identification accuracy. The whole procedure was repeated 1000 times to estimate the distribution of the identification accuracy. The identification was also performed using domain-based FNC, and results are provided in the supplementary materials.

We further performed nonparametric permutation testing to assess the statistical significance of identification accuracy. We permuted subject identity for the FNC of scans to shuffle the intra-subject and inter-subject FNC similarity. The same identification was performed 1000 times on the permuted data to have the identification accuracy for the permuted data.

Test-retest Reliability and Longitudinal Identification

We further calculated the FNC similarity between other scans (between scan 1 and scan 3, between scan 1 and scan 4, and between scan 1 and scan mean [mean FNC across scans 2~4]) from the baseline session. We also calculated the FNC similarity between scans from the second-year session. The same

identification was performed using the FNC similarity between scans. To investigate whether the FNC profile can identify an individual from a longitudinal scan while there are developmental changes in the brain, we measured the FNC similarity between a scan from the baseline session and a scan from the second-year session and then performed the identification based on the FNC similarity between longitudinal scans.

Cognitive Measures

The *cross-scan* FNC stability was measured by the intra-subject similarity between FNC of scan 1 and mean FNC across scans 2~4. To show the test-retest reliability of the associations, we also replicated the results using different FNC stability measures and using the second-year data. Details of the replication can be found in the supplementary materials.

We first investigate the associations between FNC stability and cognitive assessments. The cognitive performance of each adolescent was measured via the NIH Cognition Battery Toolbox (abcd_tbss01) [29]. Higher scores indicate better cognitive performance. The NIH neurocognitive battery contains 7 distributional characteristics, including the Toolbox Picture Vocabulary Task (TPVT), the Toolbox Oral Reading Recognition Task (TORRT), the Toolbox Pattern Comparison Processing Speed Test (TPCPST), the Toolbox List Sorting Working Memory Test (TLSWMT), the Toolbox Picture Sequence Memory Test (TPSMT), the Toolbox Flanker Task (TFT), and the Toolbox Dimensional Change Card Sort Task (TDCCS). There are also 3 composite scores, including a Crystalized Intelligence Composite and a Fluid Intelligence Composite, and a Total Score Composite. In total 10 cognitive scores were used in the analysis. The detailed information of each score can be found in [29].

Mental Problem Measures

The associations between *cross-scan* FNC stability and children's mental health conditions were also investigated. The mental health conditions of children were measured by the Parent Child Behavior Checklist Scores (abcd_cbcls01). These checklist scores contain 11 syndrome scales related to psychiatric problems and 1 total Syndrome Scale, 6 DSM-Oriented scales, and 3 CBCL Scale2007 Scales. In total 20 scores from the Parent Child Behavior Checklist Scores were used for the investigation. The ABCD Parent General Behavior Inventory-Mania (abcd_pgbi01) was also used to assess the subsyndromal mania. It contains 10 scores that evaluate the children's behaviors of mania. Higher scores of the mental health measures indicate dimensional psychopathology.

Sleep Conditions and Screen Usage

The assessments of sleep conditions and sleep disorders of children were measured by ABCD Parent Sleep Disturbance Scale for Children (abcd_sds01). It includes 26 questionnaires to evaluate the sleep

disturbance of each child. For example, question 1 is “How many hours of sleep does your child get on most nights?” and question 2 is “How long after going to bed does your child usually fall asleep?”. The scores will be between 1 to 5, with a higher score indicating a worse sleep condition (e.g., fewer hours of sleep and longer time to fall asleep). The screen time utilization of youth, which is measured by the ABCD Youth Screen Time Survey (abcd_stq01) was also used to investigate its relationships with *cross-scan* FNC stability. It contains 14 scores that evaluate the screen usage of a child during the weekdays and weekends, with higher scores indicating longer screen usage.

Parental Behaviors and Prenatal Exposure

We were also interested in the potential relationships between parental factors and the children’s FNC stability. The prenatal exposure before and during pregnancy, measured by ABCD Developmental History Questionnaire (dhx01) was used for the investigation. We focused on prenatal exposure to tobacco, alcohol, and marijuana, and the parents’ age when the child was born. The parent dimensional psychopathology, measured by ABCD Parent Adult Self Report Raw Scores Aseba (pasr01), was also used in the analysis. These scores evaluate parent dimensional psychopathology from either positive question (e.g., question q15: I am pretty honest) or negative question (e.g., question q12: I feel lonely). The higher scores in the positive question indicate better condition of parents while the higher scores in the negative question indicate worse dimensional psychopathological condition.

Association between *Cross-scan* FNC Stability and Behaviors

An LMM was adopted to investigate the associations between intra-subject *cross-scan* FNC stability and the behavioral assessments. The LMM was also used to examine the associations between the children’s FNC stability and their parents’ conditions and neighborhood safety. The ABCD data contain related data at sites and within families due to twins and siblings. The LMM can model families nested within the site to take account of this effect. It has been successfully applied in previous ABCD studies and identified meaningful brain-wide associations with a wide range of individual behaviors [37,38]. In this work, *cross-scan* FNC stability was modeled as the dependent variable, while each score/behavior was modeled as a fixed effect. Age, gender, race, height, and weight that were considered as confounding effects were modeled as other fixed effects. The family structures and sites were modeled as random effects [37]. The correlation r-value, t-statistic, and effect size Cohen’s d was obtained for each association analysis to reflect the relationship between FNC stability and a behavioral score. The results are corrected by false discovery rate (FDR) correction [39].

Abbreviations

ABCD = Adolescent Brain Cognitive Development; AUD = auditory domain; CB = cerebellum domain; CC = cognitive control domain; DM = default-mode domain; FC = functional connectivity; FDR = False discovery rate; FNC = functional network connectivity; fMRI = functional magnetic resonance imaging; ICA = independent component analysis; ICN = intrinsic connectivity network; LMM = linear mixed-effect model; QC = quality control; SC = subcortical domain; SM = sensorimotor domain; TC = time-course; TDCCS = Toolbox Dimensional Change Card Sort Task; TFT = Toolbox Flanker Task; TLSWMT = Toolbox List Sorting Working Memory Test; TORRT = Toolbox Oral Reading Recognition Task; TPCPST = Toolbox Pattern Comparison Processing Speed Test; TPSMT = Toolbox Picture Sequence Memory Test; TPVT = Toolbox Picture Vocabulary Task; VS = visual domain

Declarations

Data Availability

The code of Neuromark framework and the Neuromark template have been released and integrated in the group ICA Toolbox (GIFT, https://trendscenter.org/software/gift/), which can be downloaded and used directly by users worldwide. The ABCD data used in the present study can be accessed upon application from NDA. Other MATLAB codes of this study can be obtained from the corresponding author with reasonable request.

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Author Contributions

Zening Fu and Vince Calhoun designed the study; Zening Fu performed the data analysis; Zening Fu, Jingyu Liu, Jing Sui, and Vince Calhoun wrote the paper. Mustafa Salman helped with data preprocessing. All authors contributed to the results interpretation and discussion.

Competing Interests

The authors declare no competing interests.

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Figures

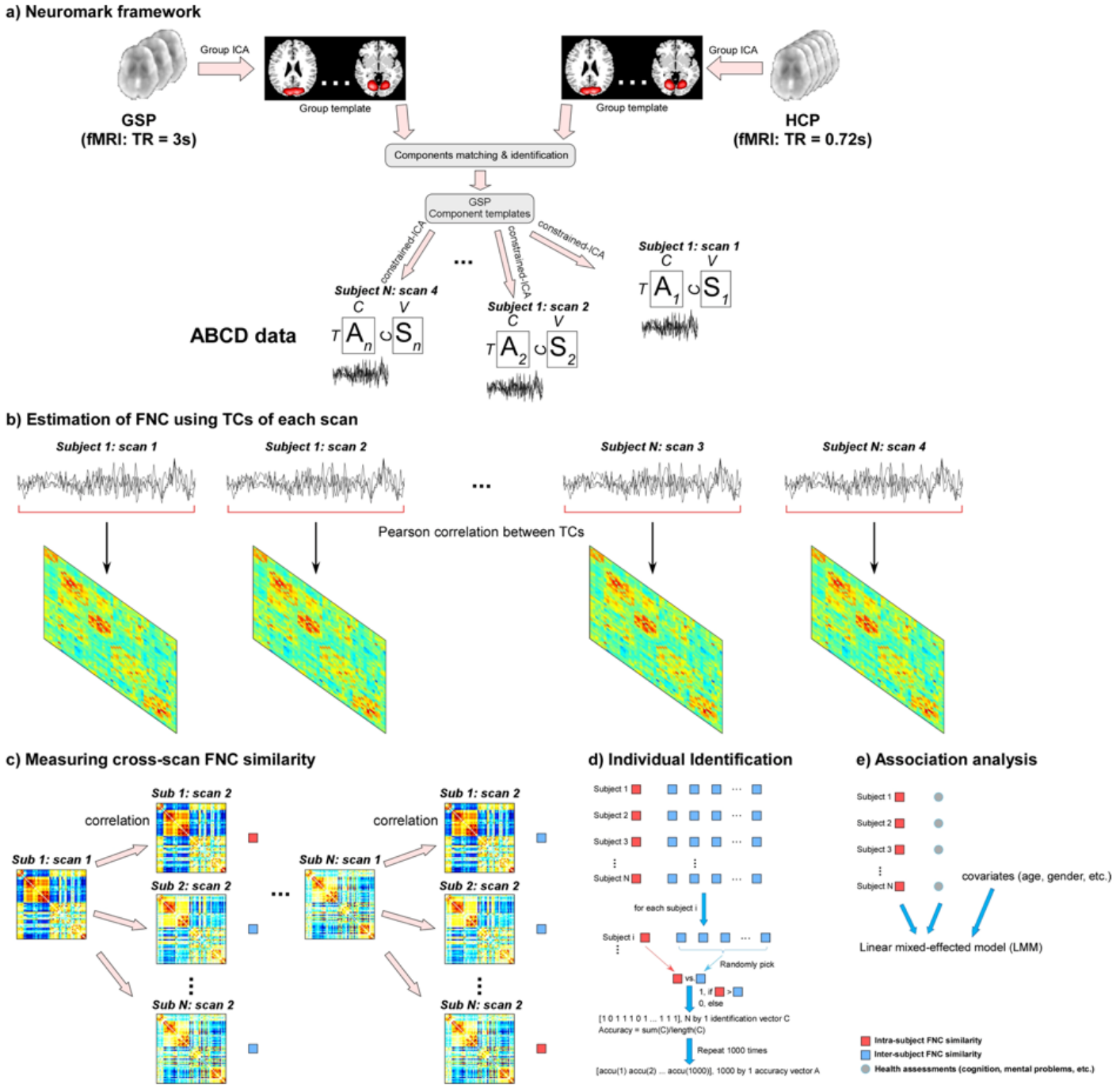

Figure 1

The flowchart of the FNC analysis to investigate cross-scan FNC stability and variability. a) Neurmark framework extracts robust functional components from the ABCD data. **b)** FNC is estimated using the TCs of components from each scan. **c)** *Cross-scan* FNC similarity is measured by the correlation between FNC from different scans. **d)** Individual identification is performed based on the cross-scan FNC similarity. **e)** Association analysis between intra-subject FNC stability and individuals' behaviors via the LMM.

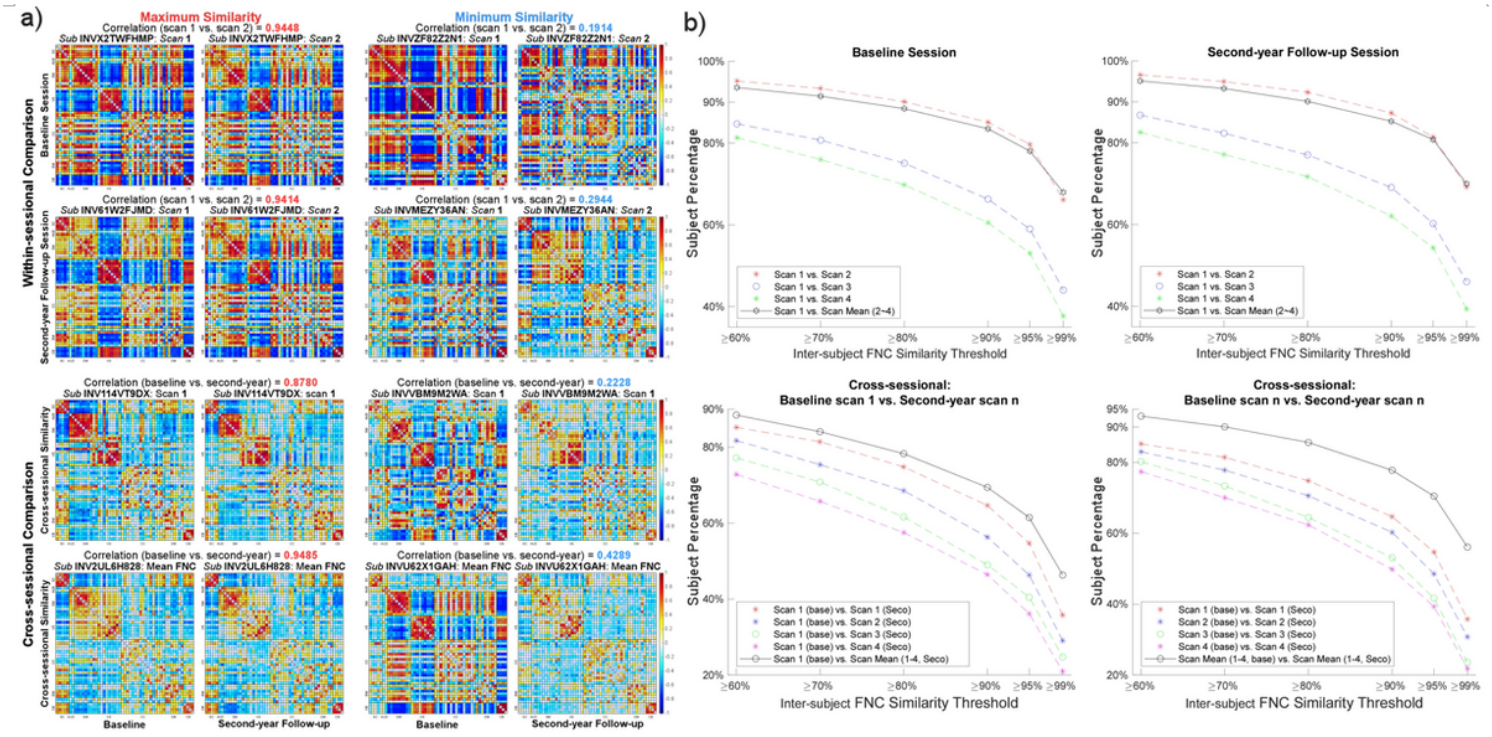

Figure 2

***Cross-scan* FNC similarity within the same session and between longitudinal sessions.** FNC similarity is calculated using scans 1) within the baseline session; 2) within the second-year session; and 3) between longitudinal sessions. **a)** Subjects with the maximum and minimum FNC similarity within the baseline, the second-year follow-up and cross-sessional. **b)** Percentage of subjects with intra-subject FNC similarity larger than a given percentage of inter-subject FNC similarity. Higher intra-subject FNC similarity is observed between scans from the same session. Intra-subject FNC similarity between longitudinal sessions is higher if FNC is averaged across scans.

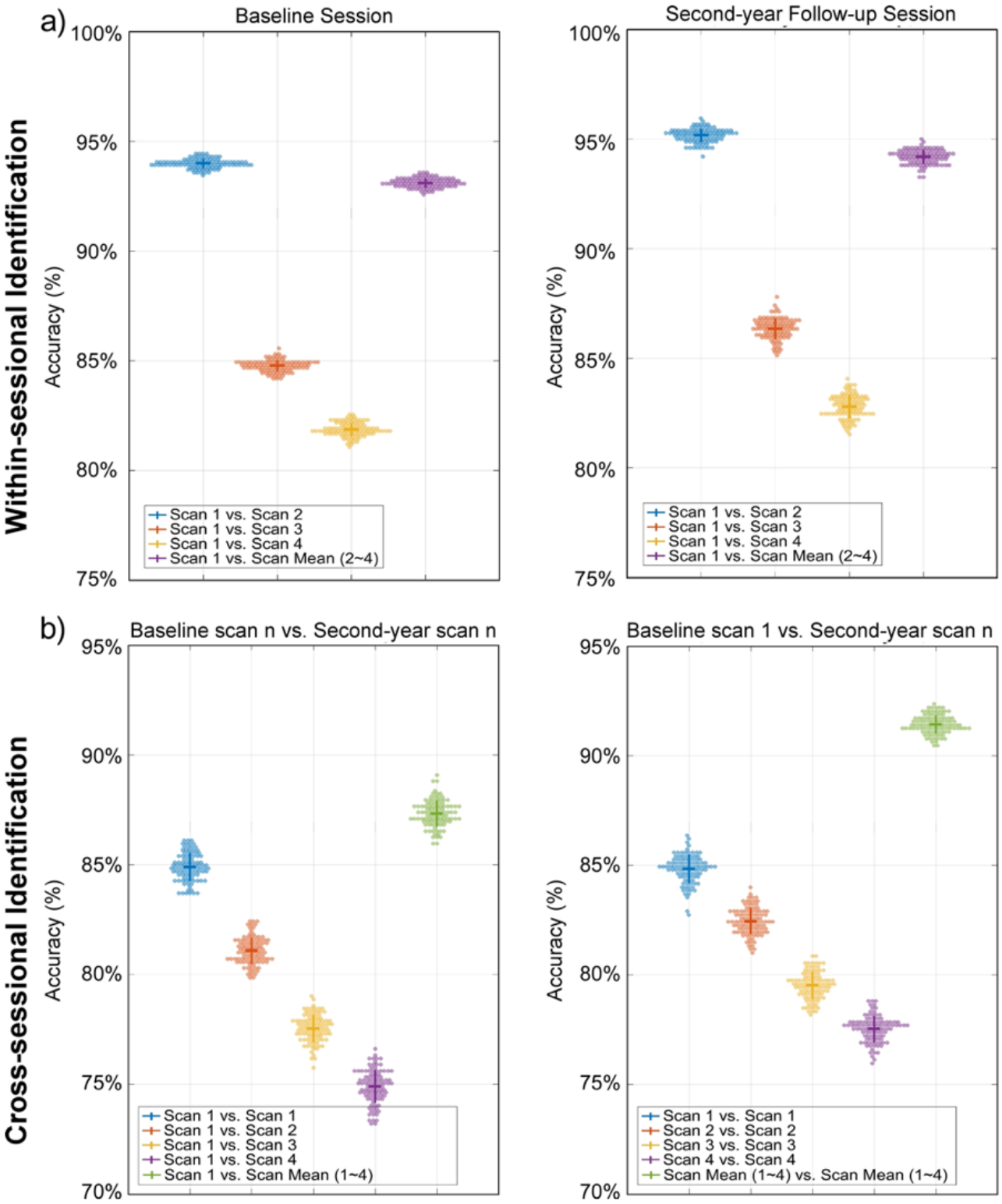

Figure 3

Individual identification using FNC across scans. a) Identification accuracy based on the FNC similarity between the scans within the baseline session. Scan 1 is the database while other scans are the target. Individual identification is replicated using FNC of scans within the second-year session. **b)** individual identification is performed between scans from longitudinal sessions. Scans from the baseline session are the database and scans from the second-year session are the target. Identification accuracy drops

when developmental brain changes are introduced. Averaging FNC across scans within each session can improve the performance of longitudinal identification.

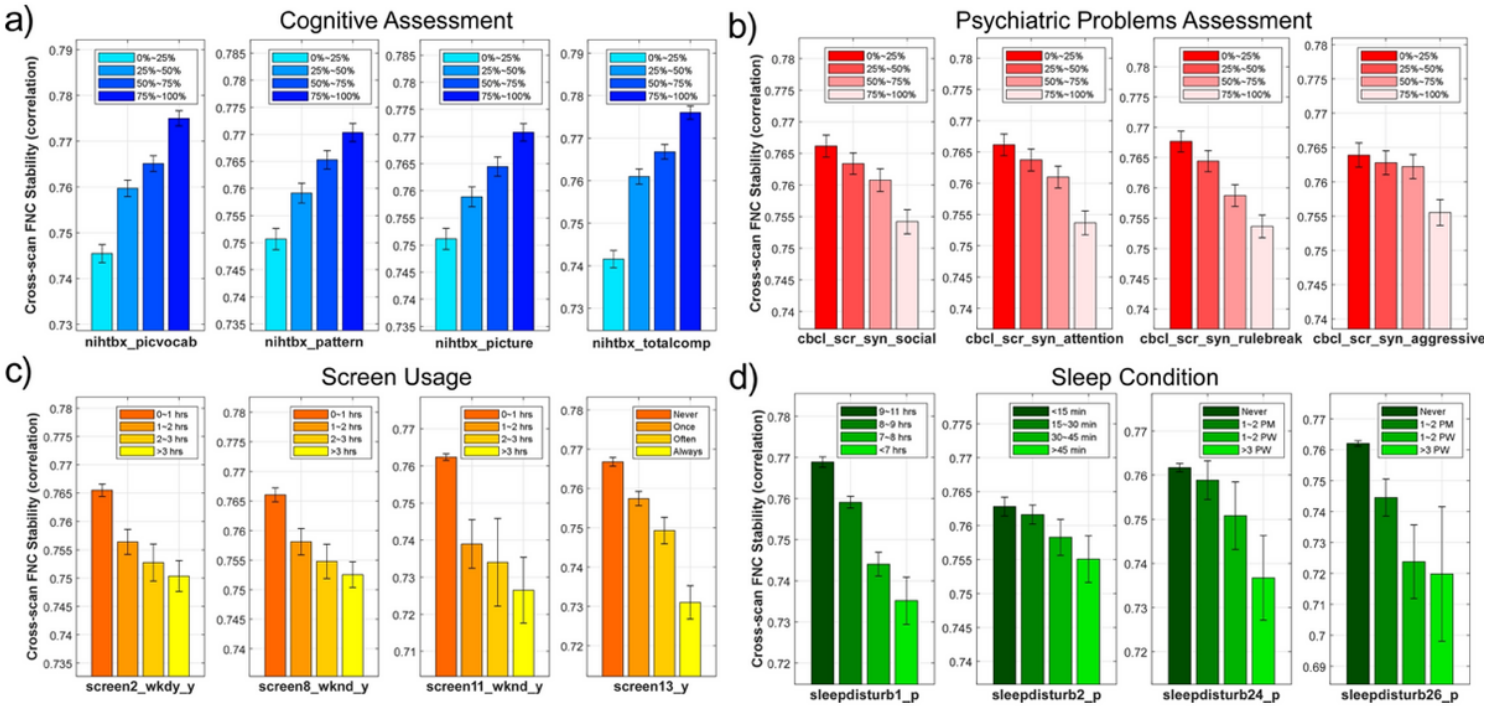

Figure 4

Cross-scan **FNC stability predicts children's behaviors.** The bar is the mean of FNC stability and the error bar is the standard error of the mean (SEM) of FNC stability. **a)** Positive relationships between FNC stability and cognitive measures (FDR corrected, $q < 0.05$). Children with good cognitive performance tended to have higher *cross-scan* FNC stability. **b)** Negative relationships between FNC stability and psychiatric problem scores (FDR corrected, $q < 0.05$). Children with high psychiatric problem scores tended to have lower *cross-scan* FNC stability. **c)** Negative relationships between FNC stability and the children screen usage (FDR corrected, $q < 0.05$). Children with more screen usage (e.g., longer time watching TV and video) tended to have lower *cross-scan* FNC stability. **d)** Negative relationships between FNC stability and the children's sleep condition. (FDR corrected, $q < 0.05$). Children with bad sleep conditions (e.g., shorter sleep duration and longer time to fall asleep) tended to have lower *cross-scan* FNC stability.

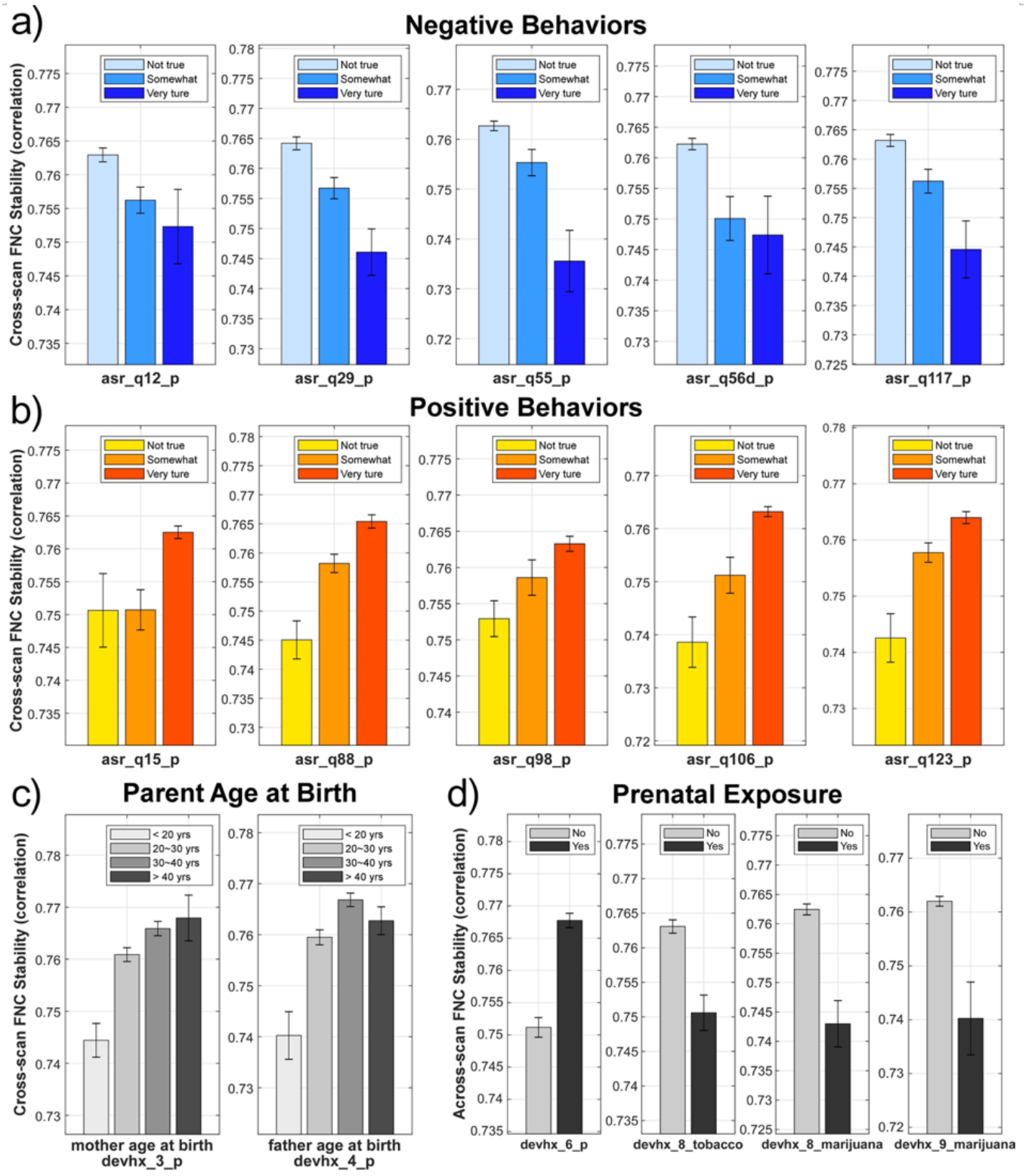

Figure 5

Children's FNC stability is associated with developmental history and their parents' dimensional psychopathology. a) Negative relationships between children's FNC stability and their parents' negative behaviors (e.g., question q12: I feel lonely). Children with parents having negative psychopathology tend to have lower *cross-scan* FNC stability. **b)** Positive relationships between children's FNC stability and their parents' positive behaviors (e.g., question q15: I am pretty honest). Children with parents having positive

behaviors tend to have higher *cross-scan* FNC stability. **c)** Relationships between FNC stability and parents' age at birth. The parents' age is positively correlated with children's FNC stability. **d)** Relationships between FNC and prenatal exposure. Prenatal exposure to tobacco and marijuana is associated with lower *cross-scan* FNC stability in children.

Supplementary Files

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