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Functional Connectivity Stability: A Signature of Neurocognitive Development and Psychiatric Problems in Children*

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***Abstract*— Brain functional connectivity has been shown to provide a type of fingerprint for adult subjects. However, most studies tend to focus on the connectivity strength rather than its stability across scans. In this study, we performed for the first time a large-scale analysis of within-individual stability of functional connectivity (FC) using 9071 children from the Adolescent Brain Cognitive Development database. Functional network connectivity (FNC) was extracted via a fully automated independent component analysis framework. We found that children's FNC is robust and stable with high similarity across scans and serves as a fingerprint that can identify an individual child from a large group. The robustness of this finding is supported by replicating the identification in the two-year follow-up session and between longitudinal sessions. More interestingly, we discovered that the within-individual FNC stability was predictive of cognitive performance and psychiatric problems in children, with higher FNC stability correlating with better cognitive performance and fewer dimensional psychopathology. The overall results indicate that the FNC of children also shows reliable within-individual stability, acting as a fingerprint for distinguishing participants, regardless of significant growth and development in the children's brain. FC stability can be a valuable imaging marker to predict early cognitive and psychiatric behaviors in children.**

***Clinical Relevance*—The stability of functional connectivity can be used to identify children from a large group and to draw inferences on early-age cognitive and psychiatric behaviors.**

I. Introduction

The human brain shows remarkable variability in time and across populations [1]. Derived from functional magnetic resonance imaging (fMRI) data, functional connectivity (FC) has shifted focus away from exploring regional brain activity toward characterizing co-activation across distributed brain regions [2]. Although neuroimaging studies have revealed a great deal of knowledge of brain functional organizations, their findings are typically limited to drawing inferences on general patterns across a group of subjects [3] or comparing brain changes or abnormalities across populations [4].

An adult's FC profile is believed to be unique, regardless of how the brain is engaged during the scanning [5], [6], acting as a "fingerprint". Unlike adults, adolescents can be more "variable", with continuous growth and development inside their brains [7], which may result in more within-individual heterogeneity on FC. By incorporating young populations, recent research has shown that FC fingerprints can identify both youths and adults with similar performance [8]. Despite such progress, we argue that the exploration of within-individual FC stability has some limitations. First, these studies used a relatively small number of participants (i.e., sample size < 500) and failed to examine the robustness of their findings across scans from longitudinal sessions. Second, prior results were mostly based on atlas-derived FC measures, which did not consider the variations of functional brain regions across scans. Third, previous work ignored the biological basis of within-individual FC stability, and thus the neural mechanisms under the FC stability are still far from understood. Therefore, there is the need for a reliable study that includes a large sample size of children data with multiple scans collected from longitudinal sessions for a comprehensive examination of the relevance of variations in FC stability to individual differences in behaviors.

To address the above, in this work, we investigated the within-individual FC stability in children using a large-scale multimodal database called Adolescent Brain Cognitive Development (ABCD). The ABCD database includes more than 11,800 children and collected a comprehensive range of measures related to mental problems, cognitions, and other healthy backgrounds. Our hypothesis is twofold. On one hand, we predicted that children's FC profile demonstrates reliable within-individual stability across scans and between longitudinal sessions, regardless of substantial development in the brain. On the other hand, within-individual FC stability might be associated with behavioral phenotypes in children, such as cognitive performance and psychiatric problems.

II. Methods

A. Participants and Behavioral Assessments

This work is based on the release 2.01 of the ABCD dataset, which contains over 11,800 children aged between 9-10 years old (baseline), and with multiple scans from two imaging sessions (baseline and the second-year follow-up). The ABCD database incorporated a comprehensive range of demographic data on each participant, including neurocognitive battery, physical and mental health assessments, and other health backgrounds. The parent's full written informed consent and the child's assent were obtained under protocols approved by the Institutional Review Board.

B. Preprocessing and Subject Selection

We downloaded the raw fMRI data and preprocessed the data using a combination of FMRIB Software Library v6.0 (FSL) toolbox and Statistical Parametric Mapping 12 (SPM) toolbox. Details of the ABCD data can be found at the National Institute of Mental Health Data Archive (https://nda.nih.gov/).

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The fMRI data underwent preprocessing procedures including rigid body motion correction, distortion correction, normalization to standard Montreal Neurological Institute (MNI) space, and smoothing using a Gaussian kernel with a full width at half maximum (FWHM) = 6 mm.

Quality control (QC) of the preprocessed data was done by comparing the individual mask with the group mask. Participants with good normalization of the fMRI images were retained for further analysis. We selected subjects with at least four resting-state scans within either session. These criteria yield 9071 subjects for the baseline analysis, 2918 subjects for the second-year analysis, and 2290 subjects (with four scans sequential collected) for the cross-session analysis.

C. Neuromark Framework

We applied a fully automated independent component analysis (ICA) framework (namely Neuromark) to the ABCD data to extract functional brain regions and their corresponding time-courses (TCs) [9]. This framework was applied to each scan (5 min) of each subject, resulting in 53 intrinsic connectivity networks (ICNs) that are corresponding and comparable across subjects, sessions, and scans. The effectiveness of the Neuromark has been fully demonstrated in previous studies with numerous brain markers and abnormalities identified in different populations [9], [10]. Pearson correlations between TCs were calculated to measure the functional network connectivity (FNC) for each scan.

D. Similarity of FNC and Individual Identification

We measured the correlation between the whole-brain FNC (1378 pairs of FNC) from scan 1 and scan 2 to evaluate the similarity of FNC. If the scans are from the same subject, the correlation represents the within-individual similarity (stability) of FNC. If the scans are from different subjects, the correlation represents the between-individual similarity of FNC. For each subject, we have one within-individual correlation and 9070 between-individual correlations. Then we calculated the percentage of subjects with the within-individual correlation larger than a given percentage of between-individual correlations. To show the test-retest reliability, we repeated the same examination by calculating the correlations between different scans from the same session, and between scans from different sessions (e.g., scan 1 from the baseline vs. scan 1 from the second-year).

We further performed individual identification using the correlations of FNC. For each subject, we randomly picked one between-individual correlation from the total 9070 between-individual correlations and compared it with the within-individual correlation of this subject. If the within-individual correlation is larger, we consider that this subject is successfully identified. This step was performed for every subject and the total identification accuracy (%) was calculated. We then repeated this procedure 100 times to estimate the distribution of the identification accuracy.

E. Predictions of Cognitive Behaviors and Mental Problems

The National Institutes of Health (NIH) cognition battery toolbox, which contains 7 components, including language vocabulary knowledge, attention, cognitive control, working memory, executive function, episodic memory, and language was used in the present study to evaluate the cognitive performance of children. The Parent-Child Behavior Checklist Scores which contains 8 empirically-based syndrome scales related to psychiatric problems, including anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, and summarized internalizing broadband score, and externalizing broadband score, and a psychiatric problems total score were used in the present study to evaluate the dimensional psychopathology of children.

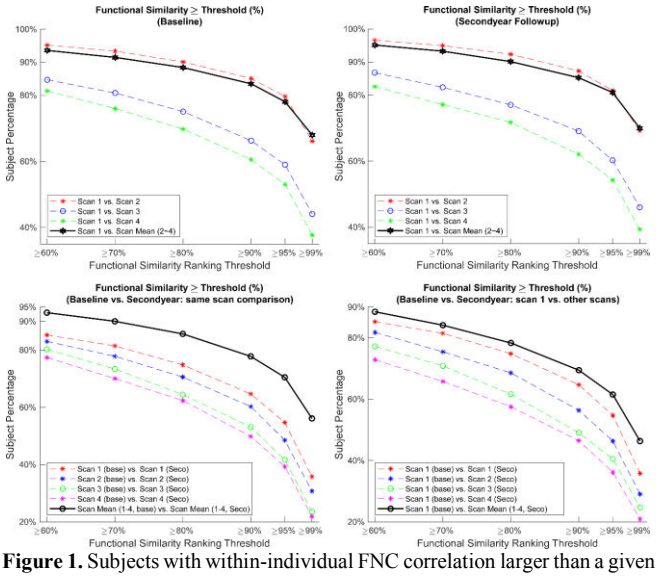

Figure 1. Subjects with within-individual FNC correlation larger than a given percentage of between-individual FNC correlations.

A linear mixed-effect model (LMM) was used to explore the associations between stability of FC (within-individual correlation of FNC) and 1) the children's cognitive scores and 2) the children's psychiatric problems. LMM will take account of the correlated observations within families due to twins and siblings and at sites. In this model, within-individual correlation of FNC was modeled as the dependent variable, while each target score was modeled as a fixed effect. Potential confounding effects, including age, gender, race, height, and weight were modeled as other fixed effects. The family structures nested within sites were modeled as random effects.

III. Results

A. FNC Shows High Within-individual Stability

Fig. 1 displays the results of the percentage of subjects with the within-individual correlation of FNC larger than a given percentage of between-individual correlations. The top left panel is the result for the baseline session and the top right panel is the result for the second-year session. The highest within-individual stability is observed between FNC from scan 1 and scan 2.

Take the red line of the top left panel for example, more than 70% of children have a within-individual correlation of FNC larger than 99% of between-individual correlations of FNC, while more than 95% of subjects have a within-individual correlation of FNC larger than 60% of between-individual correlations of FNC. The results are consistent across sessions, with similar stability of FNC in the baseline and second-year sessions respectively.

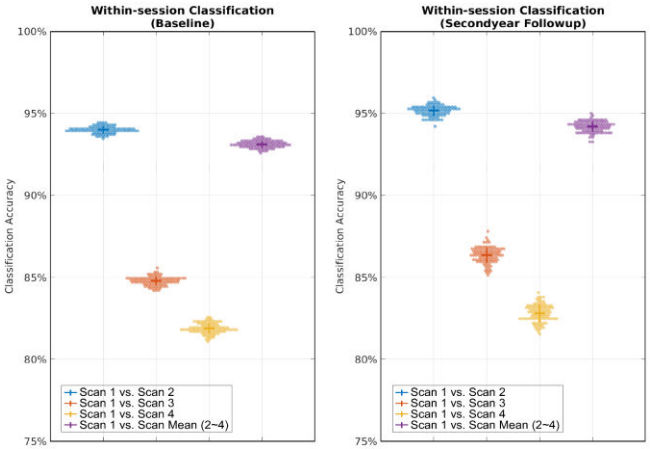

Figure 2. Identification results based on the correlations of FNC between scans within same session.

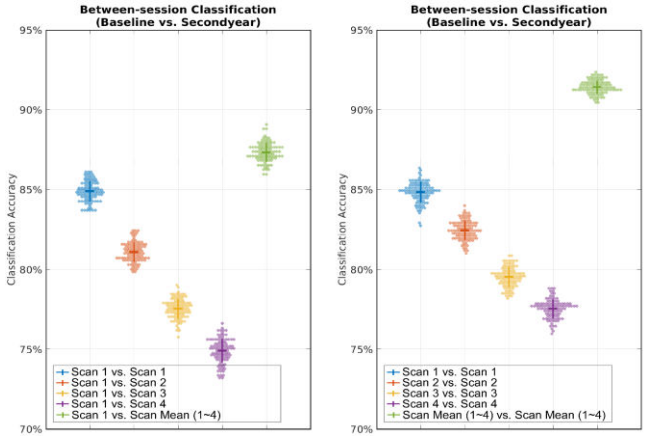

Figure 3. Identification results based on the correlations of FNC between scans from longitudinal sessions.

Individual's FNC is also highly stable between scans from longitudinal sessions. The bottom panels of Fig. 1 display the results of FNC similarity between the baseline and the second-year sessions. Although greater time intervals between sessions incurred a decrease in within-individual FNC stability, the within-individual correlation is larger than the majority of between-individual correlations of FNC, especially when FNC was averaged across scans (black lines).

B. Individual Identification using FNC stability

Fig. 2 provides the results of the individual identification using FNC of scans from the same session. For the baseline session, the averaged identification accuracy was 93.99%, 84.78%, 81.87%, and 93.10% using correlations between FNC from scan 1 and scan 2, between FNC from scan 1 and scan 3, between FNC from scan 1 and scan 4, and between FNC from scan 1 and mean FNC across scans 2~4, respectively. Similar results can be observed at the second-year session, with 95.16%, 86.35%, 82.80%, and 94.18% identification accuracy.

The identification was then performed using FNC correlations of scans from longitudinal sessions. Although the scans from longitudinal sessions might capture development changes in children's FNC, the individual's FNC still showed reliable stability across scans that can be used for the identification of a child from a large group. Results showed an identification accuracy between 74.91%~91.43%, with the highest accuracy (91.43%) obtained by examining the correlations of mean FNC (averaged across scans, Fig. 3).

C. Higher Within-individual FNC Stability is Associated with Better Cognitions and Fewer Psychiatric Problems

The within-individual correlation between FNC from scan 1 and mean FNC across scans 2~4 at the baseline session was used for the investigation. 10 out of 10 of the cognitive summary scores were positively correlated with within-individual FNC stability (false discovery rate [FDR] corrected, $q < 0.05$). The association results are provided in Table I, with the range of r values between 0.0376 and 0.1070. To better visualize the results, we divided the children into four groups from low cognitive performance to high cognitive performance, according to each cognitive score. Fig. 4 displays the positive associations between within-individual FNC stability and cognitive measures. Children with good cognitive performance tended to have higher within-individual connectivity stability.

Meanwhile, 12 out of 20 psychiatry problems scores show significantly negative associations with within-individual FNC stability, with r values ranging from -0.0257 to -0.0496 (FDR corrected, $q < 0.05$, Table II). Fig. 5 shows that children with high psychiatric problems scores tended to have lower within-individual connectivity stability.

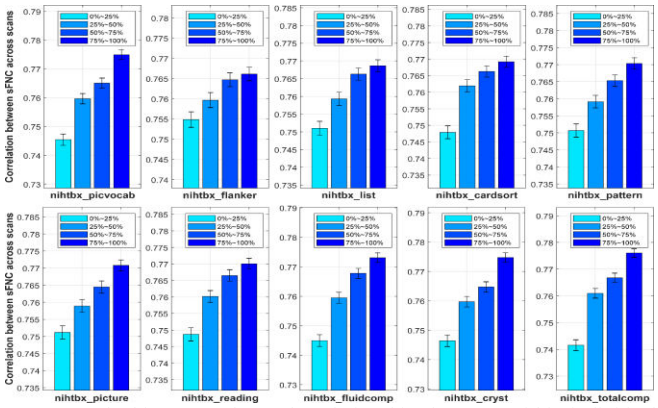

Figure 4. The histogram shows the relationships between within-individual FNC stability and cognitive measures. Children with good cognitive performance tended to have higher FNC stability.

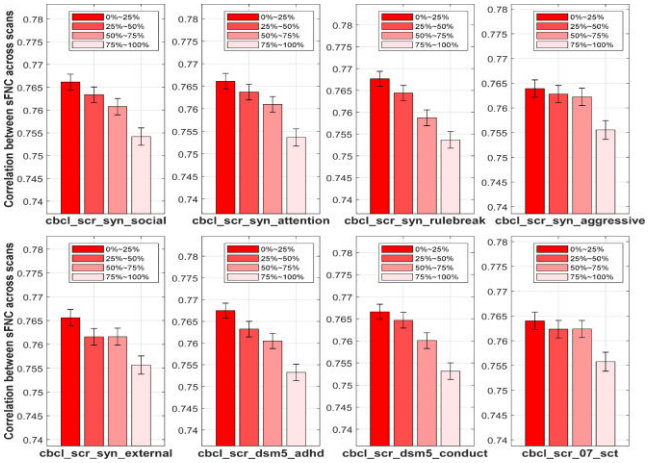

Figure 5. The histogram shows the relationships between within-individual FNC stability and psychiatric problems scores. Children with high psychiatric problem scores tended to have lower FNC stability.

TABLE I. FNC STABILITY CORRELATED WITH COGNITION

NIH TB Summary	r value	Cohen's d	p value
nihtbx_picvocab	0.0841	0.1688	1.54e-15
nihtbx_flanker	0.0376	0.0753	3.68e-4
nihtbx_list	0.0547	0.1096	2.35e-7
nihtbx_cardsort	0.0603	0.1208	1.14e-8
nihtbx_pattern	0.0662	0.1326	3.78e-10
nihtbx_picture	0.0624	0.1250	3.45e-9
nihtbx_reading	0.0671	0.1344	2.13e-10
nihtbx_fluidcomp	0.0911	0.1830	7.36e-18
nihtbx_cryst	0.0865	0.1737	2.53e-16
nihtbx_totalcomp	0.1070	0.2152	4.82e-24

TABLE II. FNC STABILITY CORRELATED WITH PSYCHOPATHOLOGY

Behavior Checklist	r value	Cohen's d	p value
cbcl_scr_syn_social	-0.0496	-0.0992	2.38e-6
cbcl_scr_syn_thought	-0.0257	-0.0514	0.0145
cbcl_scr_syn_attention	-0.0471	-0.0944	7.25e-6
cbcl_scr_syn_rulebreak	-0.0481	-0.0963	4.64e-6
cbcl_scr_syn_aggressive	-0.0387	-0.0774	2.31e-4
cbcl_scr_syn_external	-0.0425	-0.0850	5.25e-5
cbcl_scr_syn_totprob	-0.0332	-0.0664	0.0016
cbcl_scr_dsm5_depress	-0.0309	-0.0618	0.0033
cbcl_scr_dsm5_adhd	-0.0452	-0.0904	1.70e-5
cbcl_scr_dsm5_opposit	-0.0319	-0.0638	0.0024
cbcl_scr_dsm5_conduct	-0.0467	-0.0935	8.82e-6
cbcl_scr_07_sct	-0.0354	-0.0709	7.51e-4

IV. DISCUSSION

Neuroimaging studies have successfully established that adults' FC profiles show substantial within-individual stability, which can be leveraged for identifying a given individual from another scan [5], [6]. However, whether changes in brain development during adolescence will introduce more within-individual variability in FC that impact individual identification has not been well studied, which can be challenging due to confounding effects often observed in children's scans (e.g., head motion) [11]. Our present work used a comprehensive analysis and found that children's FC has robust stability across scans, even when the scans are from longitudinal sessions with a two-year interval. The children's FC can be used for the subject identification, although the overall accuracy dropped as the interval of scans increased. Our finding is in line with a previous study based on a relatively small sample size, which suggested that the larger time intervals can introduce more variability between sessions that incurred a decrease in identification [8].

More interestingly, we found that within-individual FC stability is not trivial but informative, linked to children's behaviors. Specifically, higher within-individual FC stability is associated with better cognitive performance and fewer psychiatric problems in children. Spontaneous FC dynamics can relate to the performance of numerous cognitive tasks [12]. Existing literature has shown that individuals with more similar FC across time had a better cognitive performance, as measured by increased accuracy and more stable response times [13]. Our results extend these findings by showing that individual FC profile exhibits robust stability across scans, and the degree of stability is associated with cognitive behaviors. A growing body of literature has linked the increased functional network reconfiguration and temporal disorganization of FC to psychiatric diseases [14], [15]. Consistent with these findings, our results suggest that the variability of an individual's FC can also be prominent across scans, and such within-individual heterogeneity of FC can predict early psychiatric problems in adolescents.

V. CONCLUSION

The present study reveals that the child's FC shows substantial stability across scans and even between longitudinal sessions. The within-individual FC stability is significantly associated with children's cognitive performance and psychiatric behaviors. This is the first large-scale investigation of the cross-scan FC stability and its potential as a brain marker of early cognitive developments and mental health in children. It provides a critical foundation for future work to novel test inferences about how single-subject brain FC stability relates to behavioral phenotypes.

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