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# Discovery and Replication of Time-Resolved Functional Network Connectivity Differences in Adolescence and Adulthood in over 50K fMRI Datasets

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*Abstract*— **There remains an open question about whether and in what context brain function varies in adolescence and adulthood. In this work, we systematically study the functional brain networks of adolescents and adults, outlining the significant differences in the developing brain detected via time-resolved functional network connectivity (trFNC) derived from a fully automated independent component analysis pipeline applied to resting-state fMRI data in over 50K individuals. We then statistically analyze the transient, recurrent, and robust brain state profiles in both groups. We confirmed the results in independent replication datasets for both groups. Our findings indicate a strengthening of a state reflecting functional coupling within the visual, motor, and auditory domains and anticorrelation with all other domains in a unique adult state profile, a pattern consistently less modular in adolescents. This new insight into possible integration, strengthening, and modularization of resting-state brain connections beyond childhood convergently indicates that the highlighted temporal dynamics likely reflect robust differences in brain function in adolescents versus adults.**

## I. INTRODUCTION

Adolescence is the transitory period between childhood and adulthood, characterized by crucial physical, psychological, neurobiological, sexual, social, cognitive, and emotional changes. Understanding how functional brain systems mature over the course of development in this crucial phase of life is vital to understanding healthy brain function and neuropsychiatric disorders [1]. In addition to this general evolution in the global network architecture of the brain, strengths of functional connections within brain networks also undergo substantial modifications with development. However, there remains an open question about whether and in what context the functional connections are expected to evolve from adolescence to adulthood.

Neuroimaging modalities such as magnetic resonance imaging (MRI) [2] and resting-state blood oxygenation level dependent (BOLD) functional MRI (fMRI) [3] are now increasingly used to study neurodevelopment. In the brain's resting state, individuals may typically engage in some form of unconstrained mental activity that alters the brain's functional connectivity and modular organization. Resting-state fMRI studies explore the resting brain's large-scale functional organization by viewing the brain as a complex, integrative network composed of spatially distributed but functionally interacting sub-networks that continually share and process information. The high-dimensional fMRI data is reduced in space, typically using region of interest (ROI) or atlas-based techniques or data-driven parcellation methods such as group independent component analysis (gICA) [4]. In this work, we study whole-brain functional network connectivity (FNC) amongst spatially distinct resting-state networks (RSNs) of the brain. This approach reveals how different brain networks couple to establish a specific function of the brain, typically focused on synchronous co-activation quantified through various statistical measures, including correlation, mutual information, and coherence at a static or time-varying scale.

Whole-brain FNC has traditionally been estimated using time-averaged connectivity metrics, but a more recent paradigm shift involves studies increasingly exploring the time-varying nature of these underlying fluctuations [5]. Intuitively, brain dynamics can be reasonably assumed to be even more prominent at rest as the mental activity is unconstrained. Recent evidence shows that time-resolved FNC (trFNC) is related to ongoing cognition, behavior, and phenotypic traits, and alterations in trFNC have been linked to several neurological and psychiatric conditions. trFNC approaches thus may have a great potential in characterizing differences in adolescent and adult brains, a topic that we explore in the current work.

While there are several ways to summarize the temporal dynamics of brain connectivity [6], here we focus on a data-driven approach [7] to evaluate trFNC differences in adolescents vs. adults. The approach is based on established signal processing and machine learning methods, including a fully automated group independent component analysis (gICA) approach [8] to compute RSNs that are both specific to individuals as well as comparable across datasets and subjects. We next use sliding window correlation to quantify trFNC between the RSNs, and k-means clustering to characterize the recurring, transient brain state profiles. We pursue this approach as the trFNC brain state patterns estimated with this approach are primarily reproducible across individuals and robust against variations in data attributes, as confirmed in our previous work [9]. a

In this work, we systematically investigate trFNC differences in adolescents and adults, outlining significant differences in the adolescents versus adults brain detected by our trFNC analyses on both discovery resting-state fMRI data and in replication data for both groups. Additionally, we statistically analyze the transient, recurrent, and robust brain state profiles in both groups and determine the associated summary measures to gain further complementary insights into the temporal dynamics of the developing brain. Figure 1 describes an overview of the experimental design. We discuss the materials and methods in Section II, demonstrate our critical results in Section III, discuss the key outcomes of this study in Section IV and present our conclusion in Section V.

## II. Materials and Methods

### A. Functional MRI Data

Resting-state fMRI scans (eyes open: passive crosshair viewing) from the UK Biobank (UKB: *n*=36461, *F:M*=19474:16987) [10] and the Adolescent Brain Cognitive Development (ABCD: *n*=9617, *F:M*=4722:4895) [11] studies were used for the original analyses (discovery) in this work, whereas the Human Connectome Project (HCP: *n*=833, *F:M*=439:394) [12] and the Developmental Chronnecto-Genomics (Dev-CoG: *n*=191; *F:M*=96:98) [13] studies were used for confirmatory analyses (replication). Data acquisition details can be found on the above referenced work for these datasets, and any acquisition differences were mitigated by implementing standard, thoroughly tested preprocessing, and feature extraction pipelines as detailed next. The experimental procedures involving human subjects were approved by the respective institutional review boards of all participating centers.

### B. Data Preprocessing

All datasets underwent preprocessing using standard fMRI practices, including normalization to the standard Montreal Neurological Institute (MNI) template, and smoothing using a Gaussian kernel with a full width at half maximum (FWHM) = 6mm. Quality control (QC) of the preprocessed fMRI datasets included discarding the images exhibiting a low correlation with individual and/or group level masks, shorter scan lengths, and high head motion to rule out potential spurious differences in functional connectivity. The above-stated numbers are post-QC sample sizes; only one image was used per subject in all conducted research.

### C. RSN Estimation

The next experimentation stage involved extracting resting-state networks (RSNs) and associated regional activity time-courses from the fMRI data. For that objective, we decomposed the preprocessed fMRI time-courses using spatially constrained group independent component analysis (SC-gICA) [14] using the Neuromark [8] template as reference maps (n=53 brain regions). This approach has successfully discovered shared and distinct biomarkers in several clinical populations [15] and allows us to estimate RSNs that are both specific to individual subjects and comparable to one another.

### D. Time-Resolved FNC Feature Extraction

Subsequently, we calculated the trFNC features between all ($n={}^{53}C_2=1378$) brain connections using a tapered sliding window. Lastly, we identified the recurring, transient brain state profiles for each dataset by modularizing that dataset's windowed correlations using the classical k-means clustering algorithm [7] and computed statistical state summary measures (as detailed in the following sub-section) for gaining further insights into the brain states in adolescence and adulthood.

### E. Statistical Measures

Characterizing trFNC states and summarizing statistical state measures provides insights into various aspects, including the temporal state dynamics and state transition behavior. To quantify the similarities and differences in the brain states of adolescents and adults, we computed cross-correlation between the brain state profiles estimated for both groups in the discovery and replication datasets. Additionally, we computed several state summary measures, including mean dwell times, fractional occupancy times, and state transition probabilities.

Mean dwell times are computed as the mean period of temporally consecutive runs of each state. In contrast, fractional occupancy times are calculated as the percentage of windows assigned to each state for that given scan. Finally, we captured the state transition behavior using a first-order Markov model that explains the propagation of probability transitions associated with entering and exiting the brain states.

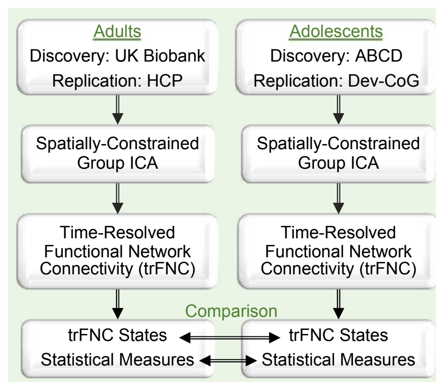


Figure 1: Study Workflow. This figure describes an overview of the experimental design. All considered datasets were decomposed using spatially-constrained group-ICA. trFNC features were estimated using the sliding window correlation approach, and then the recurring brain states were characterized using the *k*-means clustering algorithm. trFNC state profiles and derived statistical state summary measures were compared across adolescents and adults for the discovery and replication datasets.

## III. Results

### A. Brain state profiles in adolescence and adulthood

The estimated trFNC state profiles in the adolescent and adult datasets were sorted using Pearson's correlation metric. Figure 2 shows the sorted state profiles for the considered discovery and replication datasets. Of particular relevance, findings indicate strengthening of brain connections within the visual, motor, and auditory domains and anticorrelation with all other domains in State 4 for adults (Figure 2: State 4 for UKB and HCP datasets). Notably, this state profile was absent in adolescents for all clustering model orders (*k*=2 to *k*=5).

In parallel with these changes, the adults also showed strong correlation within subcortical (SC) and between SC and cerebellar (CB) regions, and anticorrelation of the SC and CB domains with visual (VIS), motor (SM), and auditory (AU) domains. This unique adult state also showed a higher correlation strength between the SC and certain regions in the cognitive control (CC) domain involving the Medial Cingulate Cortex (MCC), Inferior and Middle Frontal Gyrus (IFG and MiFG), and Hippocampus (Hipp), and likewise some default-mode regions such as the Anterior and Posterior Cingulate Cortex (ACC and PCC). Overall, the corresponding patterns were less modular for adolescents, with a visibly lower correlation strength within the VIS and SM domains and disjointed CB and SC domains.

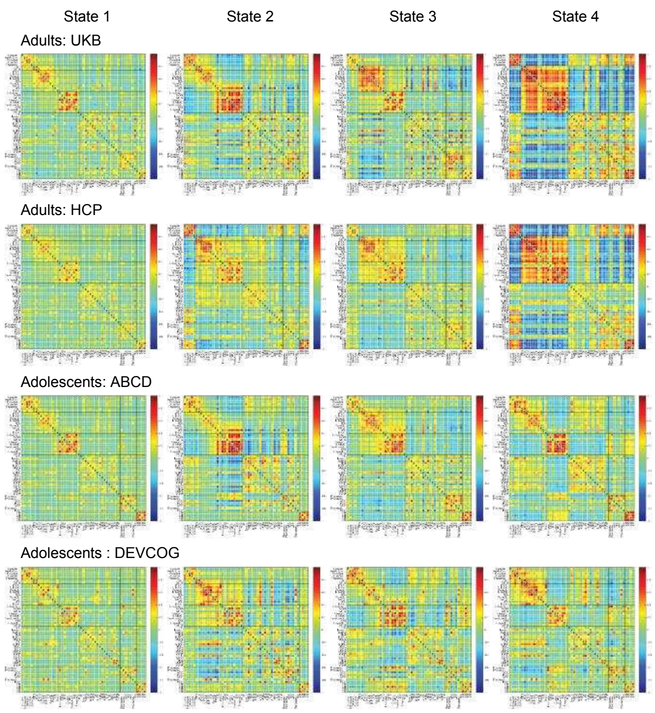


Figure 2: A comparison of time-resolved functional connectivity state profiles in adolescents and adults in multiple data sets. Of particular relevance, findings indicate a strengthening of brain connections in a unique adult brain state (State 4, top right, in the UKB and HCP panels); this pattern was consistently absent in adolescents.

## B. *Cross-correlation of brain state profiles*

Each brain state profile was correlated across both groups' discovery and replication datasets to quantify the observed similarities and differences in the state patterns and confirm the patterns inferred visually in the previous sub-section. As seen in Figure 3, this particular result highlights highly consistent differences between adolescence and adulthood in state 4. Highly similar patterns were observed across the groups for states 1 and 3. State 2 showed intermediate correlations across the groups.

## C. *Effect of difference in sample size*

Results were effectively validated for similar group sizes to reject the confound due to higher adult samples in both replication and discovery datasets. More specifically, we compared the state profiles from a random subset ($n$=9617) of the UKB dataset with those from the ABCD data ($n$=9617), and likewise a random subset ($n$=191) of HCP data with those from the Dev-CoG dataset ($n$=191). All results were held for this validatory check, and no significant effect of the difference in sample size was reported in this analysis.

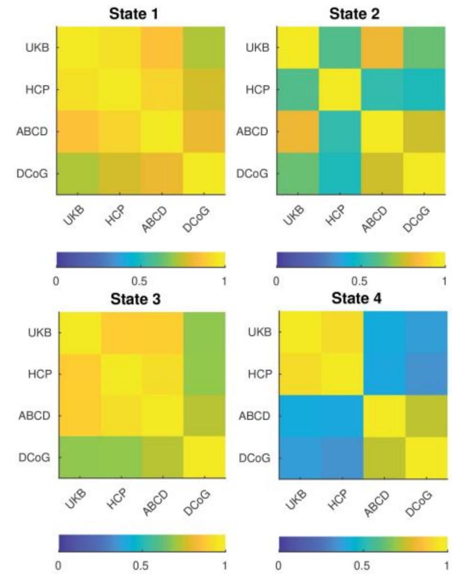


Figure 3: Pair-wise correlations of the sorted brain states. This graph distinctly highlights the low correlations in State 4 between adolescents and adults.

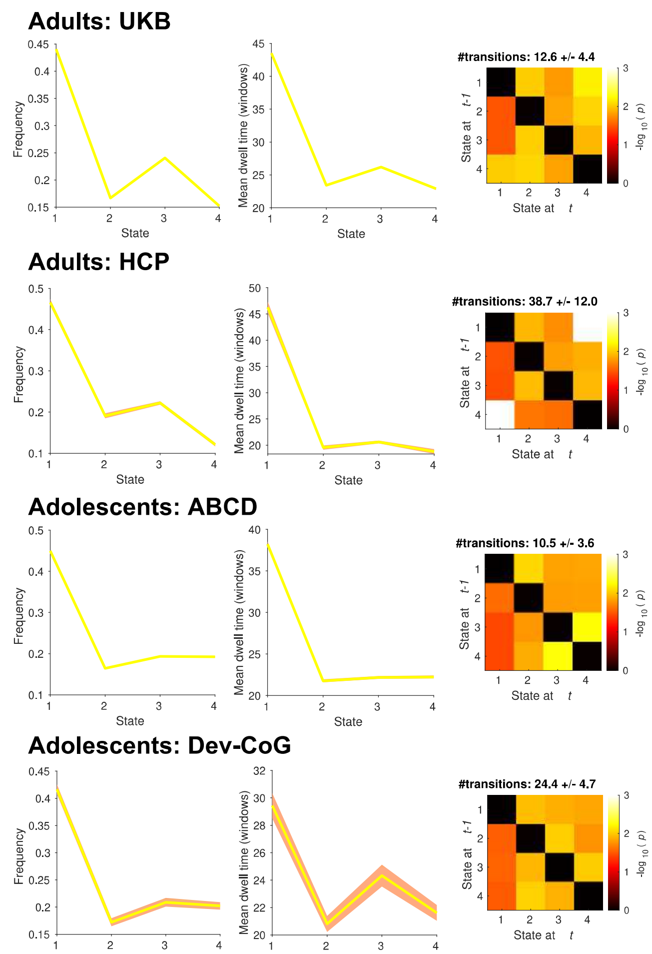


Figure 4: Temporal dynamics of functional connectivity were characterized by brain state summary measures such as average state frequency, mean dwell times, and state transition probability matrices and compared in the adolescent and adult brains.

### D. State profile statistical summary measures

State 1 was consistently the most prevalent, recording the highest average frequency and dwell-times in adults and adolescents, a trend confirmed in the replication dataset likewise. Remarkably, this state showed a flattened (i.e., disconnected) global pattern and was the most similar to the static FC patterns for all datasets. Furthermore, the other three states occurred comparably and lesser frequently than State 1. Additionally, the probability of transitioning to the unique adult state (state 4) was lowest from State 1 in both adult datasets.

## IV. DISCUSSION

The highly modular, elevated connectivity between the visual, motor, and auditory domains and anticorrelation with all other domains in one of the trFNC state profiles in adults and lack of this pattern in adolescence altogether supports the notion of strengthened motor-visual functional integration from adolescence into adulthood. Notably, a previous study [16] confirmed reduced static FC in the sensorimotor and visual systems in children as well as young adults, whereas none of the trFNC states estimated in another recent study [17] revealed elevated connectivity between these domains in adolescence. Collectively, these results provide a cohesive view into possible integration, strengthening, and modularization of sensorimotor and visual resting-state brain connections beyond childhood, signaling a change in the broader organization of the brain's functional architecture. Our results also suggest that the estimated trFNC state profiles and summary measures are robust, especially since these are highly comparable within each group and replicate in the discovery and replication datasets in most states.

Overall, findings can be perceived as convergently indicating that functional connectivity evolves during adolescence and that the highlighted temporal dynamics are likely reflective of the maturation process of human brain development in adolescence. Future work will link functional connectivity measures to anatomical measures and clinical assessments. Exploring age and gender-related effects and the role of other possible confounders, e.g., the anatomical differences in the two studied groups that may complicate the comparison, are exciting topics for future work in the domain.

## V. CONCLUSION

To conclude, it is evident from the current results that the highlighted temporal dynamics are different substantially and consistently in at least one of the trFNC state profiles in adults. This observation rationally reflects the evolving functional connectivity and a maturation process of human brain development in adolescence. Such conceptual findings can help us understand how the human brain develops and functions, providing invaluable inputs to identify biomarkers of brain disorders and diseased conditions.

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