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Childhood adversities characterize the heterogeneity in the brain pattern of individuals during neurodevelopment

Rajan Kashyap[1], Bharath Holla[2,*], Sagarika Bhattacharjee[3,*], Eesha Sharma[4,*], Urvakhsh Meherwan Mehta[5], Nilakshi Vaidya[6,7], Rose Dawn Bharath[1], Pratima Murthy[5], Debashish Basu[8], Subodh Bhagyalakshmi Nanjayya[8], Rajkumar Lenin Singh[9], Roshan Lourembam[9], Amit Chakrabarti[10], Kamakshi Kartik[11], Kartik Kalyanram[11], Kalyanaraman Kumaran[12,13], Ghattu Krishnaveni[12], Murali Krishna[14], Rebecca Kuriyan[15], Sunita Simon Kurpad[16], Sylvane Desrivieres[17], Meera Purushottam[18], Gareth Barker[19], Dimitri Papadopoulos Orfanos[20], Matthew Hickman[21], Jon Heron[22], Mireille Toledano[23], Gunter Schumann[6,24], Vivek Benegal[5] and for the Consortium on Vulnerability to Externalizing Disorders and Addictions (cVEDA)[1]

Original Article

*Equal Contribution.

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Corresponding author:
Rajan Kashyap;
Email: rajankashyap6@gmail.com;
Rose Dawn Bharath;
Email: cns.researchers@gmail.com;
drrosedawnbharath@gmail.com

Abstract

Background. Several factors shape the neurodevelopmental trajectory. A key area of focus in neurodevelopmental research is to estimate the factors that have maximal influence on the brain and can tip the balance from typical to atypical development.

Methods. Utilizing a dissimilarity maximization algorithm on the dynamic mode decomposition (DMD) of the resting state functional MRI data, we classified subjects from the cVEDA neurodevelopmental cohort ($n = 987$, aged 6–23 years) into homogeneously patterned DMD (representing typical development in 809 subjects) and heterogeneously patterned DMD (indicative of atypical development in 178 subjects).

Results. Significant DMD differences were primarily identified in the default mode network (DMN) regions across these groups ($p < 0.05$, Bonferroni corrected). While the groups were comparable in cognitive performance, the atypical group had more frequent exposure to adversities and faced higher abuses ($p < 0.05$, Bonferroni corrected). Upon evaluating brain-behavior correlations, we found that correlation patterns between adversity and DMN dynamic modes exhibited age-dependent variations for atypical subjects, hinting at differential utilization of the DMN due to chronic adversities.

Conclusion. Adversities (particularly abuse) maximally influence the DMN during neurodevelopment and lead to the failure in the development of a coherent DMN system. While DMN's integrity is preserved in typical development, the age-dependent variability in atypically developing individuals is contrasting. The flexibility of DMN might be a compensatory mechanism to protect an individual in an abusive environment. However, such adaptability might deprive the neural system of the faculties of normal functioning and may incur long-term effects on the psyche.

Introduction

The period spanning childhood, adolescence, and young adulthood is crucial since the intrinsic architecture of the brain is shaped by a wide repertoire of factors, including those that are strongly dependent on the caregiver (e.g. parents, family, guardian), experiences within educational and community settings, as well as overarching societal and cultural norms. A plethora of studies have suggested psychiatric disorders to be linked to the experiences encountered during neurodevelopment (Kim-Cohen et al., 2003; Rothbart, 2011; Shevlin, McElroy, & Murphy, 2017). There are several factors like unstable caregiving, socioeconomic situations, social disparity, stress, and frequent exposure to adversities that can lead to maladapted development (Gee, 2021; Holz et al., 2022; McLaughlin, Weissman, & Bitrán, 2019; Rakesh & Whittle, 2021; Rebello, Moura, Pinaya, Rohde, & Sato, 2018). During the developmental phase, synaptic pruning and white matter myelination play an important role in configuring the neural architecture (McLaughlin et al., 2019). These processes adapt the neural system such that the system is maximally efficient for the environment in which it is developed. These

processes are required for the healthy development of the brain, and a faultily programmed process can alter the functionality and lead to neurodevelopmental disorders (Cardozo et al., 2019; Feinberg, 1982; Germann, Brederoo, & Sommer, 2021). Studies attempt to understand these processes from a cohort of categorized healthy and diseased populations. This distinction (healthy *vs.* diseased) obscures the state of transition from healthy to disease, and the understanding of the influences that tip the balance from typical to atypical development remains limited. When population-based big neurodevelopmental data is collected without any preconceived distribution of subjects, it can be expected that brain signatures of both typical and atypical population are present in the data in the latent form. Using advance analysis techniques, these patterns can be extracted and the factors that lead to atypicality can be comprehended. In this work, we attempted to understand the point of bifurcation in the neurodevelopmental trajectory, by categorizing the neural pattern of typical and atypical development coexisting within the cohort of healthy individuals. We eventually investigated the factors that have maximal influence in altering the typical pattern of neurodevelopment, and can drive the normal pattern of development towards atypicality. At the same time, we also explored how the factor shapes the brain organization in both typical and atypical populations, and if there was any change in the pattern over the course of development (period spanning childhood, adolescence, and young adulthood).

In this aspect, resting state functional magnetic resonance imaging (rsfMRI) has the potential to reveal underlying neural organization (Biswal, Yetkin, Haughton, & Hyde, 1995; Buckner, Krienen, & Yeo, 2013; Fox & Raichle, 2007) and provide information regarding brain functions and cognitive abilities (Finn et al., 2015; Kashyap, Bhattacharjee, Yeo, & Chen, 2019a; Kashyap et al., 2019b, 2021; Kong et al., 2018; Smith et al., 2015). The information latent in the rsfMRI brain signatures can reflect our lifestyle habits, mental health conditions, and the environment we live in (Finn et al., 2015; Ikeda, Kawano, Watanabe, Yamashita, & Kawahara, 2022; Kashyap et al., 2019a, 2019b, 2021; Lake et al., 2019; Smith et al., 2015). Strategies to identify subtypes from rsfMRI by dissecting heterogeneity in the rsfMRI pattern from a large cohort and then associating the subtypes with behaviors have gained momentum (Drysdale et al., 2017; Feczko & Fair, 2020; Mattoni, Smith, & Olino, 2023). Such brain-behavior associations with subtype identification have enabled the identification of the factors that have a significant effect on mental health (Dias et al., 2015; Drysdale et al., 2017; Feczko & Fair, 2020; Mattoni et al., 2023; Zhu et al., 2022). For example, in a dataset of healthy subjects ($n = 500$) from the human connectome project (HCP, age range of 36–100 years), Smith et al. (2015) identified a positive and negative mode of variation in rsfMRI that was associated with positive (e.g. high performance on memory and cognitive test, life satisfaction) and negative (like substance use, anger, and rule-breaking behavior) spectrum of behaviors. In our previous work (Kashyap et al., 2019a), we investigated rsfMRI subtypes from 788 HCP subjects to identify behaviors that maximize the rsfMRI variance. We found that the deviations in rsfMRI pattern were associated with higher usage of marijuana, illicit drugs, alcohol, tobacco, and predisposition toward antisocial personality. These findings have enriched our understanding of the factors that can bifurcate the mental health trajectory in healthy adults. However, approximately 63% of mental illnesses begin prior to age 25, and 37% of them start before the age of 14 (McGrath et al., 2023; Solmi et al., 2022). These statistics clearly indicate that there is a need to understand the factors that dichotomize the neurodevelopmental trajectory and contribute to atypical brain development. In this aspect, leveraging the potential of previous computational techniques (applied to aging datasets) on large neurodevelopmental datasets is useful, and several studies have applied similar strategies to associate variations in the pattern of rsfMRI with behavior (Chen et al., 2022; Evans et al., 2015; Kebets et al., 2023; Lake et al., 2019; Qu et al., 2023; Sripada et al., 2020; Uddin et al., 2013). The subtle advantage of extending such techniques to early phases of development is also to map a continuum of mental health across the lifespan.

In this exploratory study, we have used our previous hypothesis-free approach (Kashyap et al., 2019a) to investigate factors that have maximal influence on variation of rsfMRI during neurodevelopment. We used rsfMRI of 987 healthy subjects, within specified age bands – children (6–11 years), adolescents (12–17 years), and young adults (18–23 years), from the Consortium on Vulnerability to Externalizing Disorders and Addictions (c-VEDA): an accelerated longitudinal cohort of children and adolescents in India (Fernandes et al., 2021; Holla et al., 2020; Sharma et al., 2023, 2020; Vaidya et al., 2023; Zhang et al., 2020). We estimated features from rsfMRIs, and classified subjects using a dissimilarity maximization algorithm that is based on the similarity/dissimilarity of their rsfMRI pattern (Kashyap et al., 2019a; Kong et al., 2018). The rsfMRI features were extracted using dynamic mode decomposition (DMD) technique (Brunton, Johnson, Ojemann, & Kutz, 2016; Rowley, Mezić, Bagheri, Schlatter, & Henningson, 2009; Schmid, 2010). Since rsfMRI contains information about the brain's static (spatial) and dynamic (time-evolving) properties, the DMD algorithm's capacity to retain the spatial- and frequency-based data characteristics has proven advantageous. Previous studies have applied this technique to rsfMRI and found spatio-temporal patterns (dynamic modes, DMs) to have enhanced associations with behaviors (Casorso et al., 2019; Ikeda et al., 2022). Here, we have used these DMs to classify subjects into two groups – one with high similarity and another with high dissimilarity between rsfMRI-features (Kashyap et al., 2019a; Kong et al., 2018). We did not formulate any directional hypothesis regarding the behavioral manifestation of rsfMRI features. So, we compared a wide range of cohort characteristics that includes scores of psychopathology, socio-economic status, social cognition, environment of home, community and school, behavioral tasks (e.g. working memory, visual attention), demographic- (age and sex), and anthropometric-parameters (e.g. height, weight) between the two groups. Subsequently, we explored how the behavioral measures that distinguished the two groups were related to differences in neural organization by correlating the behavioral scores with the DM of the brain areas. We then investigated how the correlational pattern evolved in the three age groups (childhood, adolescence, and young adulthood). Altogether, we aimed to understand the factors that differentiate typical and atypical development by capitalizing on the heterogeneity of rsfMRIs and investigating how the neural pattern is shaped in both developmental groups.

Methods

Study protocol

The cVEDA study is a cohort of about 9000 individuals (aged 6–23 years) covering a diverse population (e.g. regions with socio-

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political conflicts, migratory workers with high substance use, slum, high familial risk, urban and rural) from five geo-spatial regions of India. The Institutional Ethics Review Boards of National Institute of Mental Health and Neurosciences (NIMHANS) Bangalore, India (Item No. VII, SI. No. 7.08, Behavioral Sciences) and all other collaborating institutions approved the data collection protocol setup in accordance with the Declaration of Helsinki (1964 and later versions). A subset of 1140 subjects underwent an intensive assessment in which multiple modalities of data pertaining to (i) neuroimaging (structural-, functional, and diffusion-MRI), (ii) behavioral–phenotypic characterization (with special emphasis on externalizing behaviors), (iii) environmental exposures (psychosocial stressors, societal discrimination, nutrition and asset security, environmental toxins), and (iv) genomics (blood/buccal swab and urine) were collected. Details of the data collection procedure are available elsewhere (Fernandes et al., 2021; Sharma et al., 2023, 2020; Vaidya et al., 2023; Zhang et al., 2020). The rsfMRI's used in this study were obtained from five different 3 T MRI scanners (for details, please refer Vaidya et al., 2023) with scanning duration kept at 6 min across the sites. The cVEDA team followed a standard protocol (with structural scans based on a protocol defined by the ADNI consortium http://www.loni.ucla.edu/ADNI/Cores/index.shtml) to ensure the comparability of image-acquisition techniques and the ability to pool the multi-site MRI data. The MRI scanners engaged in the data collection for cVEDA were from Siemens and Philips. Emphasis was placed to maintain the key parameters that influence image contrast and signal to noise ratio uniform across the scanners. For rsfMRI aquisition, a gradient echoplanar imaging (EPI) sequence was utilized. To facilitate the signal equilibration, three initial dummy scans were conducted and excluded from subsequent analysis. The uniform imaging parameters across sites were as follows: voxel size set at $3.4 \times 3.4\ mm^2$, slice thickness at 2.4 mm, interslice gap of 1 mm, descending slice acquisition order, repetition time (TR) of 2200 ms, echo time (TE) of 30 ms, and a flip angle set at 75 degrees. The imaging matrix was standardized at 64×64 mm covering 40 axial slices to ensure full brain coverage. Full technical specifications are available at http://cveda-project.org/standard-operating-procedures/.

RsfMRI preprocessing

The pre-processed rsfMRI data were obtained from cVEDA's previous study (Vaidya et al., 2023). They have performed rigid body registration of each functional volume to the middle volume (FSL MCFLIRT) and applied slice-time correction (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Non-brain tissues were removed using FSLBET, and images were co-registered to high-resolution T1 image (FSL FLIRT using the BBR algorithm) (Jenkinson, Bannister, Brady, & Smith, 2002). As a part of motion correcting transformations, BOLD-to-T1w transformation and T1w-to-MNI template (MNI) warp were applied in a single step using Advanced Normalization Toolbox (ANTs v2.1.0) (Avants, Tustison, & Song, 2009). Frame-wise displacement was calculated for each functional run, and ICA-based Automatic Removal Of Motion Artifacts (AROMA) was used to generate non-aggressively denoised data (Pruim et al., 2015). A high-pass filter with a cutoff period of 125 s (<0.008 Hz) was used to remove the slow drifts and conserve high-frequency bands in the signal. Lastly, the denoized data were resampled to 2 mm isotropic and smoothed using a 4 mm non-linear filter using FSL SUSAN (Jenkinson et al., 2002). The rsfMRI time series (165 volumes) were then extracted from 116 regions using the automated anatomical labeling (AAL) atlas that consists of 90 cortical (45 for each hemisphere) and 26 cerebellar regions (Tzourio-Mazoyer et al., 2002). Therefore, the rsfMRI of a subject was 116×165 matrix.

Primary behavioral measures

The cVEDA study collected several measures for the three age bands- children, adolescents, and young adults. In this study, we considered those parameters for which data was available across the three age bands, as some questionnaires were applicable to only specific age bands (Sharma et al., 2020; Zhang et al., 2020). The parameters included data on (A) *socio-economic status*, (B) *psychopathological condition*, (C) *environmental exposure* at (i) home and neighborhood – using questionnaires from adverse childhood experiences (ACE), which includes the exposure to abuse, neglect, adversities from family and community (Felitti et al., 2019), and (ii) school – using school climate questionnaires (SCQ) (Bochaver, Korneev, & Khlomov, 2022); and (D) *executive abilities tasks* that measured – (i) risk taking propensity – using the balloon analogue risk task (BART) (Lejuez et al., 2002), (ii) response-inhibition using stop signal task (SST) (Logan & Cowan, 1984), (iii) visual attention using trail making test (TMT) (Piper et al., 2012), (iv) cognitive flexibility – using card sorting test (Berg, 1948), (v) visuospatial-attention and working memory – using CORSI block tapping task (Corsi, 1972; Kessels, van den Berg, Ruis, & Brands, 2008), (vi) short-term memory – using the digit span test (DST) (Croschere, Dupey, Hilliard, Koehn, & Mayra, 2012), (vii) theory-of-mind and social perception – using Social Cognition Rating Tools in the Indian Setting (SOCRATIS) (Mehta et al., 2011). The list of behavioral measures with a brief explanation is available in Table 1 (also see supplement). The anthropometric parameters include height (in cm), weight (in kg), body mass index, leg length (in cm), and circumference of head and mid-arm (in cm). The demographic measures included the age and sex of the subjects. Altogether, 43 cohort characteristics (measuring socio-economic status-1, psychopathology-1, environmental experiences-11, cognition & task performance-22, anthropometry-6, and demography-2) that were available across a total of 987 subjects were analyzed.

Extraction of rsfMRI features/dynamic modes (DMs)

The DMD algorithm was originally developed to understand fluid dynamics, and the details are described in the methodological papers (Brunton et al., 2016; Kutz, Brunton, Brunton, & Proctor, 2016; Rowley et al., 2009; Schmid, 2010). It has also been applied to rsfMRI to extract features for biomarker development (Casorso et al., 2019; Ikeda et al., 2022). DMD is a dimensionality reduction approach that builds on the power of singular value decomposition to provide the spatio-temporal features of the multidimensional data (see supplement). The low-rank eigen-decomposition technique in DMD computed eigenvectors and corresponding eigenvalues from rsfMRI data (Casorso et al., 2019; Ikeda et al., 2022). Eigenvectors (i.e. spatial characteristics) represent dynamic modes (DMs), which are coherent spatial structures, and the corresponding eigenvalues (i.e. temporal characteristics) represent the frequency. Studies have shown that DM obtained with all the frequency bands combined has higher associations with the behaviors (Ikeda et al., 2022), and the

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Table 1. Primary cohort characteristics considered in the present study

Measure	Number of variables	Description
Wealth Index	1	Measures of standard of living, which incorporate variables such as consumer goods ownership and key housing characteristics like water source and toilet facilities, were calculated using Principal Component Analysis coefficients from the National Family Health Survey-4.
General psychopathology factor	1	Screening questions from the Mini International Neuropsychiatric Interview version 5, which correspond to the primary diagnostic criteria of psychiatric disorders, were used to derive a general latent measure of psychopathology via bifactor Confirmatory Factor Analysis (Sharma et al., 2020; Zhang et al., 2020)
Adverse Childhood Experiences (ACE)	6	Measures the frequency of adversity experiences, and level of family cohesion. Scores for abuse, neglect, and adversities faced in the family and community are included.
School Climate Questionnaire (SCQ)	5	Evaluates perceived safety, order, support, acceptance, equity, fairness, and encouragement of autonomy in school.
Balloon Analogue Risk Task (BART)	9	Tracks the number of pumps made on collected and popped trials and total balloon burst in three colors (blue, orange, yellow) with increasing mean breaking point.
Stop Signal Task (SST)	1	Monitors the final rate of successful stops in the task. Measures the ability to stop a response that has already been initiated.
Trail Making Test (TMT)	3	Measures reaction times for different segments of the task: 'test', 'letters', and 'numbers and letters'.
Card Sorting Test	2	Captures the total of correct and perseverative responses.
CORSI Block Tapping Task	2	Measures spatial working memory with forward and backward span.
Digit Span Task (DST)	2	Measures auditory working memory forward and backward span.
Social Cognition Rating in the Indian Setting (SOCRATIS)	3	Involves recognition of faux pas in social situations and first and second-order theory of mind.

complementary information about individual differences leads to improved classification accuracy (Huang et al., 2019). Therefore, the DM (116×1 matrix) was obtained for each individual across the complete range of frequency.

Determining subjects with atypical DM pattern

Initially, all the subjects ($n = 987$) were considered as one group and the DM of every subject was obtained. The subjects were then classified based on the similarity/dissimilarity in the pattern of the DM (Kashyap et al., 2019a; Kong et al., 2018). To determine this, we correlated DMs across subjects using Pearson's correlation and obtained a 987×987 DM-correlation matrix. To select a subset of subjects with dissimilar patterns, we randomly picked an entry in the DM-correlation matrix (representing a pair of subjects) whose absolute correlation was less than a threshold of 0.80 (see supplement for other thresholds). We continued adding new random subjects, such that each newly added subject was minimally correlated (absolute $r < 0.80$) with the current set of subjects. The procedure terminated when no more subjects could be added. The procedure was repeated 5000 times, resulting in 5000 sets with varied numbers of subjects per set. Of these 5000 sets, we chose the set containing subjects with the smallest maximum absolute correlation. This subset of subjects formed the dissimilar-rsfMRI-pattern group, and the remaining subjects constructed the similar-rsfMRI-pattern group.

Brain-behavior associations

The present study employs a data-driven, bottom-up approach, where we begin by investigating variations in brain feature patterns and subsequently explore how these differences might be manifested in behavior. Therefore, after classifying the subjects with similar and dissimilar patterns of rsfMRI we identified traits that distinguished the groups by performing two-tailed t test with Bonferroni correction across the 43 parameters (measuring socio-economic status, psychopathology, environmental exposure at home/school/society, cognition and task performance, demography, and anthropometry).

We then analyzed the potential influence of the differentiating factors on the resting brain features in both similar- and dissimilar-rsfMRI-groups. To this, we correlated (r) the DMs of the brain areas (that are different between the two groups) with the scores of the behavioral measure that differentiated the two groups. To trace how these relationships evolved with age, we conducted separate correlations for children (6–11 years), adolescents (12–17 years), and young adults (18–23 years). The procedure was repeated for both sexes as well.

Exploratory and additional behavioral measures

With a similar approach, in our previous work on HCP adults, we found the subjects in the dissimilar group to have higher usage of marijuana, illicit drugs, alcohol, and tobacco, with problems of antisocial personality (Kashyap et al., 2019a). Interestingly, the c-VEDA team have also provided similar estimates related to clinical assessment (using the Mini-International Neuropsychiatric Interview, and Strengths and Difficulties Questionnaire), externalizing behavior and psychopathology including substance use behavioral addictions (a total of 41 measures, see supplement) (Sharma et al., 2020; Zhang et al., 2020). Naturally, it became interesting to explore whether

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these behaviors are also significant in neurodevelopment. To this, for each behavioral measure we removed the subjects with missing data from both the groups (similar- and dissimilar-rsfMRI) and performed two-tail t test with Bonferroni's correction.

Data and code availability

The public dataset cVEDA is available at https://cveda-project.org/. The code of DMD can be downloaded at https://faculty.washington.edu/kutz/page26/. The code for classification is also available at https://github.com/suklamaa/Maximizing_Dissimilarity_in_fMRI.

Results

DM spatial maps

The spatial map of averaged DM across subjects ($n = 987$) is shown in Fig. 1a. We extracted subjects with a dissimilar pattern of rsfMRI from the DM correlation matrix. A total of 178 subjects formed the dissimilar-rsfMRI-pattern group (max $r = 0.79$), and the remaining 809 subjects formed the similar-rsfMRI-pattern group (max $r = 0.99$). For the dissimilar-rsfMRI-pattern group, the number of subjects in the three age bands were- children = 50, adolescents = 59, and young adults = 69. Similarly, for the similar-rsfMRI-pattern group, number of children, adolescents, and young adults were 173, 342, and 294, respectively. The two groups differed in the distribution of the DM ($p < 0.05$, Bonferroni corrected) across a set of 18 brain areas located bilaterally in the (i) frontal regions that comprise frontal supra orbital (FSO), frontal mid orbital (FMO), and frontal inferior orbital (FIO); (ii) parietal regions that include mid cingulum (MC), cuneus (Cun), and precuneus (PreCun); and (iii) temporal regions with three areas temporal pole superior (TPSup), temporal pole mid (TPMid), and inferior temporal lobe (ITL). The location of these areas in the brain is shown in red, pink, and blue colored dots, each representing the areas specific to frontal, parietal, and temporal regions (Fig. 1). For the similar-rsfMRI-pattern group, the DMs (mean ± S.D.) across the subjects for the 18 bilateral areas were (i) left-FSO (−0.04 ± 0.00), right-FSO (−0.04 ± 0.00); (ii) left-FMO (−0.06 ± 0.00), right-FMO (−0.06 ± 0.00); (iii) left-FIO (−0.06 ± 0.00), right-FIO (−0.06 ± 0.00); (iv) left-MC (−0.10 ± 0.00), right-MC (−0.10 ± 0.00); (v) left-Cun (−0.11 ± 0.01), right-Cun (−0.12 ± 0.01); (vi) left-PreCun (−0.11 ± 0.01), right-PreCun (−0.11 ± 0.00); (vii) left-TPSup (−0.06 ± 0.00), right-TPSup (−0.06 ± 0.00); (viii) left-TPMid (−0.05 ± 0.01), right-TPMid (−0.05 ± 0.01); and (ix) left-ITL (−0.05 ± 0.00), right-ITL (−0.05 ± 0.01). Similarly, for the dissimilar-rsfMRI-pattern group, the DMs (mean ± S.D.) for 18 bilateral areas were (i) left-FSO (−0.05 ± 0.01), right-FSO (−0.04 ± 0.01); (ii) left-FMO (−0.06 ± 0.01), right-FMO (−0.06 ± 0.01); (iii) left-FIO (−0.07 ± 0.00), right-FIO (−0.06 ± 0.00); (iv) left-MC (−0.09 ± 0.00), right-MC (−0.09 ± 0.00); (v) left-Cun (−0.11 ± 0.01), right-Cun (−0.11 ± 0.01); (vi) left-PreCun (−0.11 ± 0.01), right-PreCun (−0.10 ± 0.00); (vii) left-TPSup (−0.06 ± 0.00), right-TPSup (−0.06 ± 0.00); (viii) left-TPMid (−0.05 ± 0.00), right-TPMid (−0.05 ± 0.01); and (ix) left-ITL (−0.06 ± 0.00), right-ITL (−0.06 ± 0.01). This has been shown in Fig. 1b (i and ii) for the areas in the left and right hemispheres, respectively. These areas are a part of the default mode network of the brain (Buckner, Andrews-Hanna, & Schacter, 2008).

Behavioral association

The scores of 43 cohort characteristics were compared between the dissimilar- and similar-rsfMRI pattern groups (see supplement). We found two behavioral measures (adversity frequency and abuse) to survive the significance level with Bonferroni's correction ($p < 0.05$). This suggested that frequent adversities encountered during the developmental phase significantly influence the resting state pattern as evaluated from the rsfMRI (Fig. 1a). The similar-rsfMRI pattern group representing the typical neurodevelopment comprised subjects that had less (1.07 ± 1.23) frequent encounters with adversities compared to the dissimilar-rsfMRI pattern group (2.26 ± 2.35). The effect size, as measured by Cohen's d, was $d = 0.80$, indicating a large effect of frequent exposure to adversities on the differences in the rsfMRI pattern between the two groups during neurodevelopment. Interestingly, only the scores of abuse (that constitutes adversity) differentiated the two groups, with individuals in the similar-rsfMRI pattern group facing less abuse (−0.13 ± 1.07) compared to the dissimilar-rsfMRI pattern group (1.58 ± 1.40). The Cohen's d of 1.18 suggested the large impact abuse holds on the development of the functional architecture of the brain during growth. Statistical analysis of the additional behaviors related to externalizing and substance use was not significant (see Table 2S in supplement).

The similar-rsfMRI pattern group had 194 children, 323 adolescents, and 292 young adults. For the similar-rsfMRI pattern group, the correlation of the DMs with the frequency of adversities was significant ($p < 0.05$, Bonferroni corrected) for two frontal regions (FMO, and FIO), two parietal regions (Cun and PreCun), and one temporal region (ITL) across both hemispheres. For the children, the correlation values for the brain areas were (i) left-FMO = 0.27, right-FMO $r = 0.25$; (ii) left-FIO $r = 0.22$, right-FIO = 0.23; (iii) left-Cun $r = 0.23$, right-Cun $r = 0.25$; (iv) left- and right-PreCun $r = 0.21$; and (v) left- and right-ITL $r = 0.23$. For the adolescents, the correlation values for the brain areas were (i) left-FMO $r = 0.28$, right-FMO $r = 0.27$; (ii) left-FIO $r = 0.24$, right-FIO $r = 0.21$; (iii) left-Cun $r = 0.27$, right-Cun $r = 0.26$; (iv) left-PreCun $r = 0.22$, right-PreCun = 0.24; and (v) left-ITL $r = 0.28$, right-ITL $r = 0.26$. For the young adults, the correlation values for the brain areas were (i) left-FMO $r = 0.22$, right-FMO $r = 0.27$; (ii) left-FIO $r = 0.21$, right-FIO $r = 0.20$; (iii) left- and right-Cun $r = 0.22$; (iv) left- and right-PreCun $r = 0.21$; and (v) left-ITL $r = 0.24$, right-ITL = 0.26. Interestingly, the correlational pattern remained consistent across the three age bands (Fig. 1b). For the ease of visualization, the spatial location of the areas is mapped in Fig. 2a. The correlational pattern was also observed between the scores of abuse and the DMs. The correlation pattern remained similar as observed for frequency of adversity (so the values are not repeated) owing to high ($r = 0.60$) and significant ($p < 0.00001$) correlation between scores of abuse and frequency of adversities.

Correspondingly, the dissimilar-rsfMRI pattern group consisted of 30 children, 77 adolescents, and 71 young adults. Significant correlations ($p < 0.05$, Bonferroni corrected) of DM with adversity were observed in (i) parietal regions (MC, Cun, and PrCun) for children, (ii) frontal regions (FSO, FMO, and FIO) for adolescents, and (iii) parieto-temporal regions (MC, Cun, and PrCun; TPSup, TPMid, and ITL) for the young adults (Fig. 1c). For the children, the correlation values for the brain areas in parietal regions were (i) left-MC $r = 0.32$, right-MC $r = 0.34$; (ii) left-Cun $r = 0.51$, right-Cun $r = 0.52$; and (iii)

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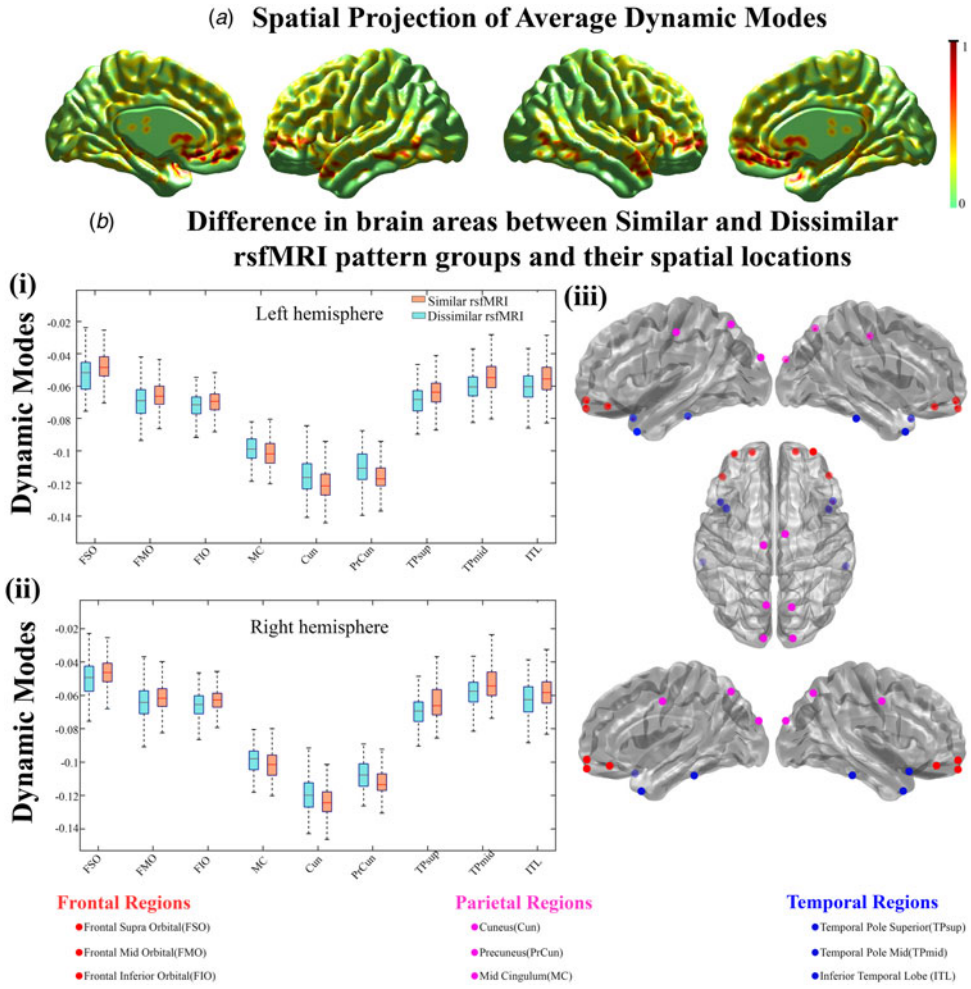

Figure 1. (a) Spatial distribution of the DMs averaged across the subjects ($n = 987$). (b) The areas showing significant differences ($p < 0.05$, Bonferroni corrected) in DMs across the three bilateral brain regions (frontal, parietal, and temporal) of the (i) left hemisphere, and (ii) right hemisphere. Each region comprises three brain areas and are shown in colored dots representing their spatial location. The frontal regions (in red dots) comprised of areas – frontal supra orbital (FSO), frontal mid orbital (FMO), and frontal inferior orbital (FIO). The parietal regions (in pink dots) consisted of Cuneus (Cun), PreCuneus (PreCun), and Mid Cingulum (MC). The temporal regions (blue dots) include the temporal pole superior (TPSup), temporal pole mid (TPMid), and inferior temporal lobe (ITL)

left-PreCun $r = 0.33$, right-PreCun = 0.36. For the adolescents, the correlation values for the brain areas in frontal regions were (i) left-FSO $r = 0.36$, right-FSO $r = 0.34$; (ii) left-FMO $r = 0.45$, right-FMO $r = 0.47$; and (iii) left-FIO $r = 0.34$, right-FIO $r = 0.37$. For the young adults, the correlation values for the brain areas in parieto-temporal regions were (i) left-MC $r = 0.37$, right-MC $r = 0.33$; (ii) left-Cun $r = 0.36$, right-Cun $r = 0.34$; (iii) left-PreCun $r = 0.35$, right-PreCun $r = 0.37$; (iv) left-TPSup $r = 0.38$, right-TPSup = 0.34; (v) left-TPSup = 0.35, right-TPSup $r = 0.36$; and (vi) left-ITL $r = 0.36$, right-ITL $r = 0.38$. The correlational pattern was also observed between the scores of abuse and the DMs. The correlation pattern trended similarly as observed for frequency of adversity (so the values are not repeated) owing to high ($r = 0.58$) and significant ($p < 0.00001$) correlation between scores of abuse and frequency of adversities. Moreover, for the two groups, there were no sex-specific signature differences in the correlational pattern of DMs and frequency of adversities.

In contrast to the similar-rsfMRI pattern group, the dissimilar-rsfMRI pattern group displayed shifts in correlational patterns across the three age bands. As illustrated in Fig. 3b, these shifts emphasize the age-related changes in neural organization resulting from ongoing exposure to adversities in different developmental windows. Specifically, the involvement of parietal region was most evident in children, the frontal region in adolescents, and both parieto-temporal regions in young adults.

Discussion

The purpose of this study was to identify the atypical signature of brain development latent within the general population, investigate the cohort characteristics associated with the atypicality, and understand how the neural system is shaped by aberrant characteristics. To this, we adopted our previous approach (Kashyap et al., 2019a) to classify the rsfMRI features (obtained from the DMD technique) of 987 subjects from the cVEDA neurodevelopmental cohort (6–23 years). Two groups with similar- and dissimilar-rsfMRI patterns ($n = 809$ and 178) emerged. The similar-rsfMRI-pattern group with a more homogenous resting state brain pattern represented typical development, and the

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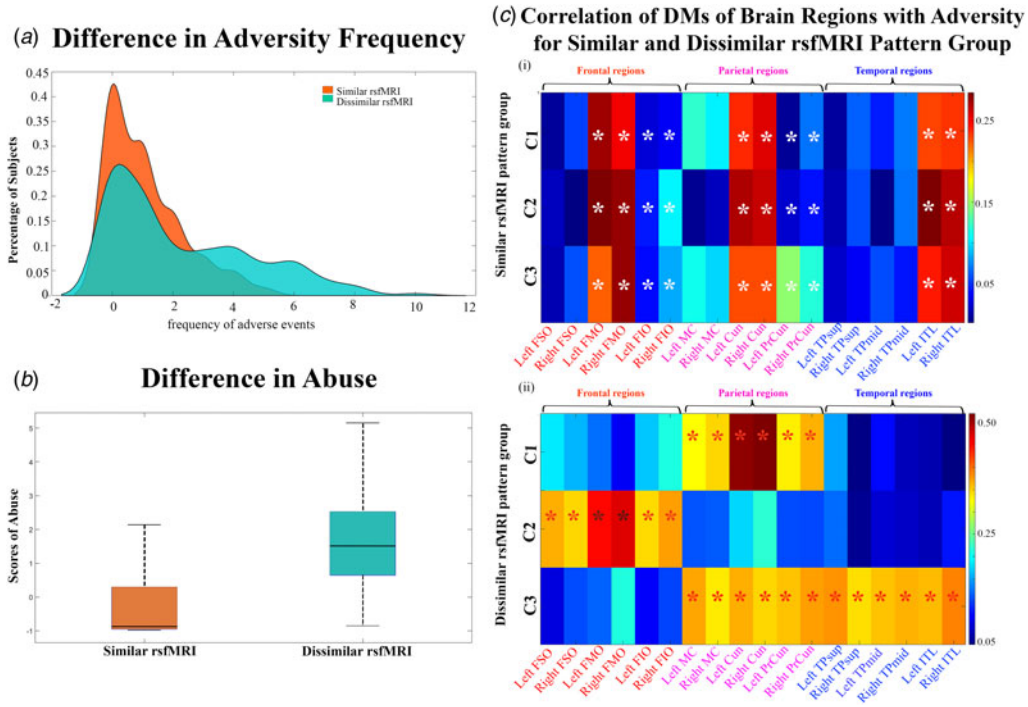

Figure 2. (a) Distribution of the frequency of exposure to adversities in the similar and dissimilar-rsfMRI pattern groups. The frequency of adversities faced by subjects in the dissimilar-rsfMRI pattern group was significantly higher ($p < 0.001$ Bonferroni corrected) than in the similar-rsfMRI pattern group. (b) The differences in the scores of abuses encountered by the two groups. The subjects in the dissimilar-rsfMRI pattern group faced significantly ($p < 0.001$ Bonferroni corrected) higher abuses. (c) The frequency of adversity was correlated with the DMs of the areas from three brain regions (frontal, parietal, and temporal). The correlational pattern is shown for both groups across the three age bands – C1 representing children (6–11 years), C2 representing adolescents (12–17 years), and C3 representing young adults (18–22 years). The correlation was significant ($p < 0.05$, Bonferroni corrected) in both hemispheres at FMO, FIO, Cun, PreCun, and ITL across the three age bands. The significant areas have been highlighted with white and red color star (*) across the two groups.

other represented an atypical pattern of neurodevelopment. The pattern showed significant differences in the 18 bilateral areas from the frontal (FSO, FMO, and FIO), parietal (MC, Cun, and PreCun), and temporal (TPSup, TPMid, and ITL) regions representing the default mode network (DMN) (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Buckner et al., 2008). Frequent encounters with life adversities distinguished the two groups, with atypicality being associated with higher frequency (seen in the dissimilar-rsfMRI pattern group). Within the parameters that constitute adversity, abuses faced during the neurodevelopmental period were of primary concern. The study is in support of the ongoing effort aimed to embrace neural heterogeneity in the population (Drysdale et al., 2017; Mattoni et al., 2023; Smith et al., 2015; Zhu et al., 2022). These studies have suggested that the hypothesis-free bottom-up approach (as adopted in our study) – wherein biological subgroups with more homogenous brain patterns across individuals are first identified, and then behavioral differences between them are examined – can provide new insights into mental health-related research and clinical practice (Fair, Dosenbach, Moore, Satterthwaite, & Milham, 2021; Feczko & Fair, 2020; Mattoni et al., 2023). Adding on, we further evaluated how the neural system has been restructured by the frequent adversities encountered by individuals of the two groups (Similar and dissimilar-rsfMRI pattern group). For this, the DMs of the DMN areas were correlated with the adversity frequency scores. While the correlational pattern in typical subjects (similar-rsfMRI pattern group) was found in frontal (FMO and FIO), parietal (Cun and PrCun), and temporal (ITL) regions, an interesting variation in the pattern with age was seen for atypical subjects (dissimilar-rsfMRI pattern group). The pattern in atypical children was clustered in parietal (MC, Cun, and PrCun) regions, subsequently shifting to frontal regions (FSO, FMO, and FIO) in adolescents, and finally simmering to parieto-temporal (MC, Cun, and PrCun; and TPSup, TPMid, and ITL) regions in young adults. The instability in the pattern provided an essence of how the brain might have adapted to adversity across the three developmental windows.

Significance of DMN and childhood adversity

Both good and bad experiences shape the human brain during development (Tost, Champagne, & Meyer-Lindenberg, 2015). The DMN involved in self-referential mental activity plays a vital role in accounting for these experiences during the early phase (Buckner et al., 2008; Davis, Hirsch, Gee, Andover, & Roy, 2022; Rebello et al., 2018). Several studies using the conventional top-down approach have reported adverse childhood experiences to be associated with structural and functional abnormalities of DMN and its interconnections with other brain areas (Hair, Hanson, Wolfe, & Pollak, 2015; Hanson et al., 2013; Sripada et al., 2020; Tottenham, 2014). There is enough support showing childhood trauma and adversities to alter DMN activity (Barch, Belden, Tillman, Whalen, & Luby, 2018; Davis et al., 2022; Holz et al., 2022; McLaughlin & Lambert, 2017; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; McLaughlin et al., 2019; Rebello et al., 2018; Zeev-Wolf, Levy, Goldstein,

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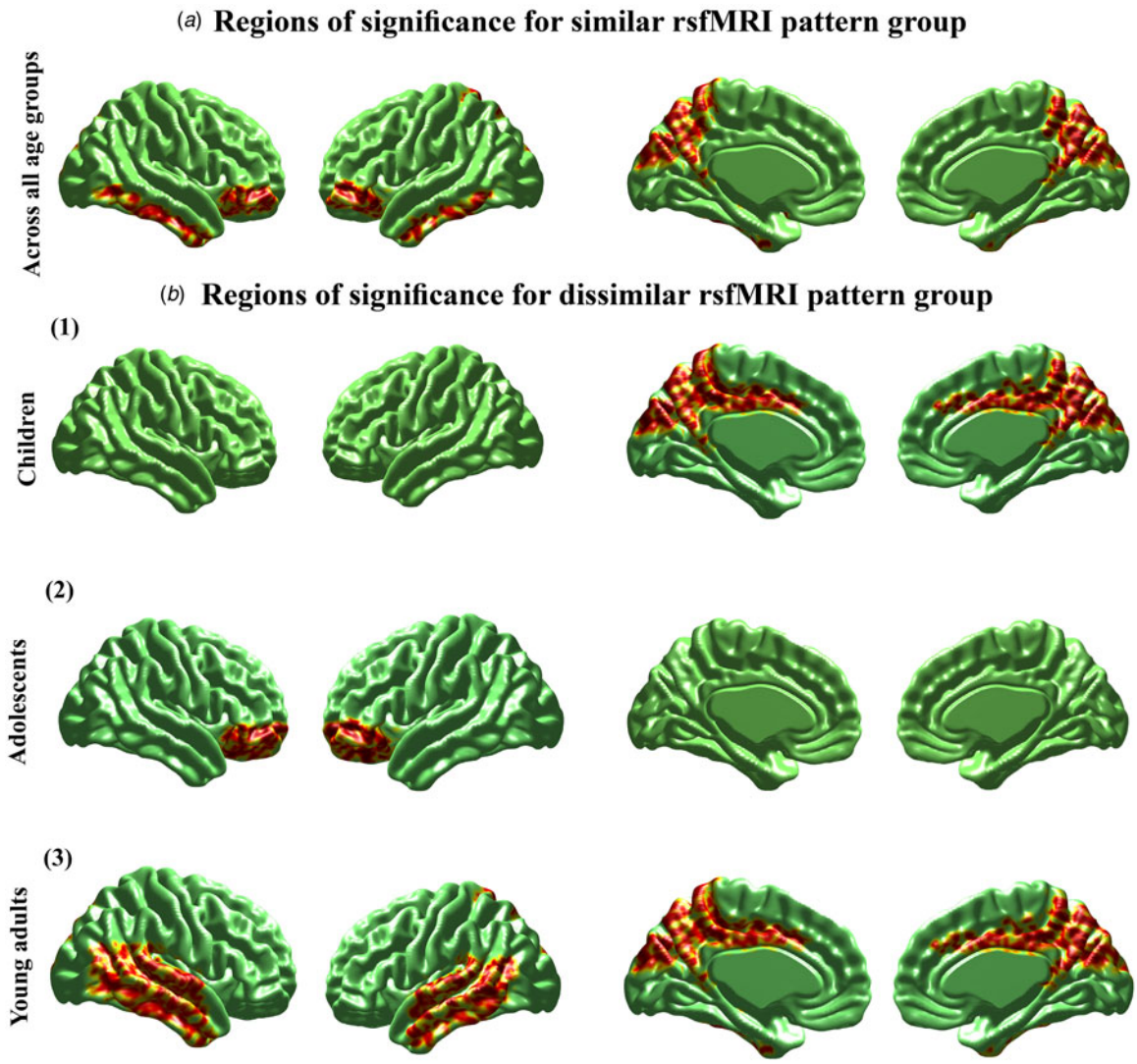

Figure 3. Shows the brain areas highlighting the correlational pattern between the DMs and frequency of adversities for the (a) similar-rsfMRI pattern group where the spatial pattern was consistent across the three age bands, and (b) dissimilar-rsfMRI pattern group where in the significant areas shifted from parietal in children, to temporal in adolescents, and parieto-temporal in young.

Zagoory-Sharon, & Feldman, 2019) and positive parenting to buffer the DMN development against environmental disturbances (Dégeilh, Bernier, Leblanc, Daneault, & Beauchamp, 2018; Whittle et al., 2017). Though a study has reported different dimensions of adversity (experiences of unpredictability, threat, and deprivation) to be related to DMN and other resting state brain networks (fronto-parietal network and salience network) (Chahal, Miller, Yuan, Buthmann, & Gotlib, 2022), in our study, only abuse emerged as a significant contributor of DMN heterogeneity. Higher adversity and abuse affect mental and physical health throughout life (Nelson, Bhutta, Harris, Danese, & Samara, 2020). As our exploratory approach also finds distinct differences in the resting state pattern to be associated with the frequency of adverse experiences and abuse, alteration of DMN can be considered as an objective marker of atypical neurodevelopment.

A similar approach, when applied to the rsfMRI dataset of aging subjects from HCP (late adulthood to old age), revealed the differences in the DMN pattern to be associated with antisocial personality, substance use, and higher consumption of alcohol, and tobacco (Kashyap et al., 2019a). A similar trend can also be observed in this study (see supplementary table 2S for the p values), though we did not observe any statistically significant difference in consumption habits and personality between the groups. This may be because of the (i) stringent criteria for statistical significance (Bonferroni's correction) adopted in the study, (ii) majority of the cVEDA subjects with imaging measures are minors and have reported no use (or minimal use) of alcohol, tobacco, and illicit drugs, and (iii) it may be too early for the manifestation of these behaviors in the features of rsfMRI. We say this because another study that considered only the young adults of cVEDA with a large sample size ($n = 9010$) found associations between adversity and predisposition toward externalizing disorders, including substance use (Fernandes et al., 2021). Similarly, several behavioral studies (using large sample sizes) have also reported significant associations between adversities of early life and antisocial personality, consumption of illicit drugs, alcohol and tobacco in later stages of life

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(Acheson, Vincent, Cohoon, & Lovallo, 2021; He et al., 2022; Krinner, Warren-Findlow, & Bowling, 2020; Lui et al., 2023; Whitesell, Beals, Mitchell, Manson, & Turner, 2009; Yazgan et al., 2021), and it can be inferred that alterations to the DMN during the early stage can have long-lasting effects on the mental health. This was also reported in a recent meta-analysis study that the neurodevelopmental period (6–25 years) is a seed time for neuropsychiatric disorders (Meredith, 2015; Solmi et al., 2022). Knotting the current findings with our previous research (Kashyap et al., 2019a), a nexus map emerges, suggesting that the neural basis of atypical behaviors is in DMN, and the environment prunes this system from early childhood. This is inline with the recent structural imaging study that investigated the neural correlates of adversity over a longitudinal period and found areas in frontal, cingulate, and limbic regions to be stable (Holz et al., 2023). Since cross-sectional data poses some limitations, future studies should apply such methodologies to longitudinal datasets to establish the continuum of mental health and illness by investigating the cumulative effect of protective- and risk-factors (e.g. education, diet, genetics, and environment) (Walhovd, Lövden, & Fjell, 2023) that fabricate the DMN from infancy (Gao, Lin, Grewen, & Gilmore, 2017; Gao et al., 2009) to maturity (Rebello et al., 2018; Washington & VanMeter, 2015) to the old age (Buckner et al., 2008; Jones et al., 2011). Altogether, the study suggests that the failure to develop a coherent DMN system due to childhood adversities might have cascading effects on an individual's trajectory of growth and aging.

The differential utilization of DMN

The sensitive period from childhood to young adulthood is where neural systems mature, including those involved in the regulation of threat, stress, and reward (Uhlhaas et al., 2023). The regions of DMN that regulate these functions undergo developmental changes over this period (Rebello et al., 2018). The network adapts according to the environment and matures accordingly (Menon, 2013). However, the knowledge about how environmental demands affect DMN maturation and how this could be related to an atypical developmental pattern is limited (Fair et al., 2010; Rebello et al., 2018). Our study finds that in typical development, there is consistency in the correlational pattern across the three age bands. This suggests that the integrity of the DMN over the developmental trajectory is crucial for the efficient processing of neural information (Sporns, 2013). The integrity of the DMN plays an important role in normal development (Raichle, 2015; Sonuga-Barke & Castellanos, 2007), and its alteration has been associated with neurocognitive disorders (Dajani et al., 2019; Fair et al., 2010; Nair, Jolliffe, Lograsso, & Bearden, 2020; Uddin et al., 2008). Several measures from graph theory (e.g. small-world topology and modularity) have found that though the neural system of typically developing children undergoes radical changes, the fundamental network characteristics seen in the brains of older children and adults get established during childhood (Menon, 2013).

In an atypical population, the correlational pattern fluctuates from parietal to frontal to parieto-temporal regions of DMN over the course of development (childhood, adolescence, and young adulthood). This is in support of a recent review article that found that exposure to stress/adversity at different sensitive periods might perturb different brain areas and affect different behaviors with different psychopathological outcomes (Andersen, 2022). It might be possible that cumulative adversity leads to the failure in the development of a coherent DMN system – a key network contributing to the emergence of efficient social information processing in the youth (Blakemore & Mills, 2014). Studies have suggested that abnormal synaptic pruning in the local circuit leads to heterogeneity in the pattern of brain functioning, a feature commonly seen in atypical development (Chattopadhyaya & Cristo, 2012; Germann et al., 2021; Gogolla et al., 2009; Patel, Leathem, Currin, & Karlsgodt, 2021). This experience-dependent plasticity, particularly during sensitive periods, may contribute to functional and structural differences in the developing brain. This can lead to differences in a variety of complex social and cognitive abilities (Barch et al., 2018; McLaughlin & Lambert, 2017; McLaughlin et al., 2015, 2019; Milbocker et al., 2021; Rebello et al., 2018). Though it is difficult to underpin the exact reason behind such a shift in the pattern with age, an underdeveloped DMN may deprive the neural system of the faculties of normal functioning. On the other hand, recent studies found the DMN and associated areas to have a protective role in coping with stress (Liu et al., 2023; Sinha, Lacadie, Constable, & Seo, 2016), though acute stress alters its processing (Zeev-Wolf et al., 2019; Zhang et al., 2019). Differential activation of these areas has also been found depending on the stress level (Sinha et al., 2016). Therefore, it cannot be denied that adversity-related neuroplasticity could also be a protective mechanism that provides the flexibility to cope with adverse environmental conditions (Sinha et al., 2016).

Altogether, the differential utilization of DMN areas emphasizes that adversity (particularly abuse) that has maximal influence in bifurcating the trajectory of development can drive the neurodevelopmental pattern towards atypicality. While typical development follows a constant pattern of utilization of DMN areas, the pattern fluctuates with age in atypical neurodevelopment. This highlights that DMN that is known to imprint the environmental cues (Rebello et al., 2018) is malleable to the situation where it develops. The adaptable nature of DMN might be a compensatory mechanism to protect an individual in an abusive environment, though such benefits are incurred at the cost of normal functioning and may have long-term effects on the psyche.

Our findings are to be interpreted within the recently proposed youth mental health paradigm (Uhlhaas et al., 2023), which emphasizes a shift from studying individuals with fully established disorders to studying emerging mental disorders or their behavioral substrates during youth. First, using a hypothesis-free bottom-up approach, we identified groups of individuals within a diverse developmental cohort that are characterized by similar or dissimilar rsfMRI patterns; these groups differed primarily on properties of brain nodes that traditionally comprise the default mode network (DMN). Second, using a statistically stringent measure, we identified a significantly greater frequency of adversities experienced, particularly that of abuse, by individuals in the dissimilar group. Lastly, we observed age-band dependent associations between functional brain features within the DMN regions – critical for social information processing, particularly in a developmental context (Blakemore & Mills, 2014) and cumulative adversity in the atypical/dissimilar group, but age-band independent associations in the typical/similar group. We did not find significant differences in cognition or psychopathology between these groups. This indicates that the evolution of DMN is an allostatic feature of environmental conditions experienced during neurodevelopment (Rebello et al., 2018). Longitudinal studies in the future will be able to reveal if adversity experiences and their neural correlates, as identified in this study can have

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cascading or domino effects in the emergence of fully established mental disorders. Together, it can be inferred that our bottom-up approach helps stratify a potentially vulnerable youth group (with greater adversity experiences) where more targeted and systematic intervention can be provided.

Conclusions

In this exploratory work, we intended to find those factors that drive neurodevelopment in India's children, adolescents, and young adults towards atypicality. Leveraging the potential of large rsfMRI datasets ($n = 987$) from the cVEDA neurodevelopmental cohort (6–23 years) we explored the heterogeneity in the brain pattern. We classified subjects based on the rsfMRI features, separating a subset with divergent patterns indicative of atypical development, while the others exhibiting similar rsfMRI patterns represented typical development. Significant contrasts emerged in regions pertaining to the DMN across these groups.

Interestingly, those exhibiting atypical rsfMRI patterns were exposed more frequently to adversities and faced higher abuses. While typically developing subjects maintained a consistent association of DMN areas with adversity across all ages, atypically developing individuals displayed variable and age-band-dependent patterns across parietal, frontal, and parieto-temporal regions, stratified by children, adolescents, and young adults. Collectively, these insights suggest that DMN's integrity is maintained during typical development, whereas recurring adversities may instigate differential utilization of the DMN, resulting in an altered pattern across different developmental stages in atypical development.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000710.

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Competing interests. The authors declare that there is no conflict of interest.

[1]Department of Neuroimaging and Interventional Radiology, National Institute of Mental Health and Neurosciences, Bengaluru, India; [2]Department of Integrative Medicine, National Institute of Mental Health and Neurosciences, Bengaluru, India; [3]Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bengaluru, India; [4]Department of Child and Adolescent Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, India; [5]Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, India; [6]Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, PONS Centre, Charité Mental Health, Germany; [7]Department of Psychiatry, Centre for Addiction Medicine, National Institute of Mental Health and Neurosciences, Bengaluru, India; [8]Department of Psychiatry, Post Graduate Institute of Medical Education and Research, Chandigarh, India; [9]Department of Psychiatry, Regional Institute of Medical Sciences, Imphal, India; [10]Division of Mental Health, ICMR-Centre for Ageing and Mental Health, Kolkata, India; [11]Rishi Valley Rural Health Centre, Madanapalle, Chittoor, India; [12]Epidemiology Research Unit, CSI Holdsworth Memorial Hospital, Mysore, India; [13]MRC Lifecourse Epidemiology Unit, University of Southampton, UK; [14]Health Equity Cluster, Institute of Public Health, Bangalore, India; [15]Division of Nutrition, St John's Research Institute, Bengaluru, India; [16]Department of Psychiatry & Department of Medical Ethics, St John's Research Institute, Bengaluru, India; [17]SGDP Centre, Institute of Psychology, Psychiatry & Neuroscience, King's College London, London, UK; [18]Molecular Genetics Laboratory, National Institute of Mental Health and Neurosciences, Bengaluru, India; [19]Department of Neuroimaging, Institute of Psychology, Psychiatry & Neuroscience, King's College London, London, UK; [20]NeuroSpin, CEA, Université Paris-Saclay, Paris, France; [21]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; [22]Center for Public Health, Bristol Medical School, University of Bristol, Bristol, UK; [23]MRC Centre for Environment and Health, School of Public Health, Imperial College, London, UK and [24]PONS Centre, Institute for Science and Technology of Brain-inspired Intelligence (ISTBI), Fudan University, Shanghai, China

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