***Childhood Adversities Characterize the Heterogeneity in the Brain Pattern of Individuals During Neurodevelopment***

**Supplemental Results**

*Dynamic mode Decomposition (DMD)*

The rs-fMRI is a high dimensional data that exhibits multiscale phenomena in both space and time. The DMD algorithm is an equation-free data-driven method that decomposes the rsfMRI in terms of its spatial structure and associated temporal responses. The fMRI time series of a subject from 𝑛 nodes (= 116) sampled every 𝑘Δ𝑡 can be represented as: (𝒙1, 𝒙2, …, 𝒙𝑚 ∈ ℝ𝑛), where Δ𝑡 represents the temporal resolution of rs-fMRI (= 2200 ms) and 𝑚 represents the number of frames (= 165).

For each subject, two data matrices X1 and X2 are created from the rsfMRI such that

𝑿1 = [ 𝒙1 𝒙2 … 𝒙𝑚−1],

𝑿2 = [ 𝒙2 𝒙3 … 𝒙𝑚],

And 𝑿2 = A𝑿1

DMD computes the leading eigendecomposition of the best-fit linear operator A using singular value decomposition. The DM are the eigen vector (𝝓𝑖) of A, and each DM corresponds to a eigen value (𝜆𝑖) associated with A. Each 𝝓𝑖 represents a coherent spatial structure whose elements are complex-valued with a magnitude (i.e., Euclidean norm) and a phase (i.e., phase shifting information). The corresponding 𝜆𝑖 represents its temporal characteristics (i.e., frequency and growth/decay).

Consequently, the rsfMRI data can be approximated as an underlying dynamic model:

where 𝑀 is the number of eigenvectors, , 𝑡 is time, and with

representing the Moore-Penrose pseudoinverse.

*Determination of Optimal Threshold*

We tested a range of thresholds to determine the subset of subjects whose rsfMRI pattern were dissimilar in the DM-correlation matrix. The thresholds were 0.70, 0.75, 0.80 (as used in the study), 0.85, 0.90 and 0.95. We repeated the dissimilarity maximization procedure to obtain the DMs across the subjects for the 116 brain regions (refer to methods section) across all the thresholded groups of subjects. The number of subjects in the subset of each threshold was 66, 106, 178 (as in the analysis), 376, 583, and 762. Threshold ≤ 0.70 were not considered because that included only 28 subjects in the dissimilar rsfMRI pattern group. On average, 92% of the total number of subjects included in a given threshold were also included in the higher thresholds. Figure S1 (A and B) illustrates the DMs of dissimilar rsfMRI pattern group across the nine (Frontal, parietal and temporal) regions of both hemispheres of DMN corresponding to a threshold. It is clear that the subset of subjects obtained with a threshold of 0.70 has non-significant (p > 0.05) difference in DMs as obtained with a threshold of 0.80 across all the regions of both hemispheres. Similarly, the subset of subjects with threshold more than 0.80 also had similar DMs like the set of subjects found with a threshold of 0.95. The threshold of 0.80 acted like a saddle point and led us to opt for this value as the optimal threshold for further behavioural evaluation.

A graph of different colored bars

Description automatically generated with medium confidence

B

A

Figure S2. Distribution of DMs across the 9 brain regions of the DMN in both hemispheres (shown in different colors). DMs distribution for threshold 0.70 is similar to 0.80 (p > 0.05). Similarly, DM distribution for thresholds above 0.80 are also similar (p > 0.05). A shift in DM distribution is significant at threshold of 0.80. So, the threshold of 0.80 was considered as an optimal choice in the study.

Moreover, the subgroups that were formed for thresholds below 0.80 manifested similar differences in the scores of behavioral measures. For example, 66 subjects formed the group when the threshold was 0.70. The subjects in this group also faced higher adversity. Interestingly, we found these subjects to be a part of dissimilar rsfMRI pattern group obtained with threshold of 0.80. Similarly, a subset of subjects with higher thresholds (≥ 0. 85) had no significant differences in the scores of behavioral measures. Altogether, the two analysis suggested for 0.80 to be considered as an optimal threshold in our study.

*Influence of head motion on the two groups*

It is important to acknowledge that head motion and physiological noise (e.g., cardiac and respiratory pulsation) can affect the interpretation of neuroimaging studies (Makowski et al, 2019). Like other studies, our artifact removal process also had certain limitations, including the absence of physiological data capture and reliance on ICA-AROMA for automatic noise identification and removal. Though we ensured through group-level ICA verification that no noise residuals remained in the data, we did not inspect individual ICs. To ensure that the interpretation of our study is not due to inherent noise in the rsfMRI data, we calculated the framewise displacement (FD) from the rsfMRI of all the subjects. We performed a two tail ttest between the similar and dissimilar rsfMRI groups. The mean ± std of FD for the similar and dissimilar rsfMRI group was 0.065 ± 0.032, and 0.067 ± 0.035 respectively, with p value = 0.460. The non-significant (p > 0.05) difference in head motion between the two groups ensured that the findings of the study were not influenced by motion-related artifacts.

*Primary Measures Across Two Groups*

The scores of the primary measures considered in the study are provided. The description of the parameters is elaborated in the main manuscript.

***Table S1****.* Averaged scores of CVEDA measures for the Dissimilar (n = 178) and the Similar-rsfMRI pattern group (n = 809).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| S.No | Behavior Category | Behavior  Name | Mean ± Standard Deviation | | *p-value* |
|  |  |  | Dissimilar rsfMRI pattern  Group | Similar rsfMRI  Pattern Group |
| 1 | Socioeconomic condition | Wealth Index | 0.29 ± 0.93 | 0.29 ± 0.91 | 0.91 |
| 2 | General psychopathology factor | Factor Analysis of psychopathological variables | 0.26 ± 1.18 | 0.17 ± 0.91 | 0.03 |
|
| 3 | Adverse Childhood Experiences (ACE) | Frequency\*\* | 2.26 ± 2.35 | 1.07 ± 1.23 | 0.000 |
| 4 | Family cohesion | 8.14 ± 57.67 | 11.84 ± 41.42 | 0.05 |
| 5 | Abuse\*\* | 1.58 ± 1.40 | -0.13 ± 1.07 | 0.000 |
| 6 | Neglect | 0.26 ± 0.48 | 0.17 ± 0.38 | 0.009 |
| 7 | Adversities in Family | 3.05 ± 1.16 | 2.29 ± 0.91 | 0.04 |
| 8 | Adversities in Community | 1.40 ± 1.23 | 1.12 ± 0.93 | 0.07 |
| 9 | School Climate Questionnaire (SCQ) | Safety | 1.11 ± 101 | -1.28 ± 115 | 0.06 |
| 10 | Order | 1.11 ± 101 | -1.28 ± 115 | 0.06 |
| 11 | Acceptance | 13.69 ± 51.3 | 9.46 ± 82.8 | 0.29 |
| 12 | Fairness | 18.85 ± 2.84 | 14.46 ± 3.8 | 0.37 |
| 13 | Autonomy | 18 ± 3.93 | 10 ± 8.30 | 0.17 |
| 14 | Balloon Analogue Risk Task (BART) | Number of Pumps collected on trials with Blue Balloons | 271 ± 200 | 270 ± 196 | 0.95 |
| 15 | Number of Pumps collected on trials with Orange Balloons | 32 ± 18 | 29 ± 18 | 0.65 |
| 16 | Number of Pumps collected on trials with Yellow Balloons | 119 ± 46 | 124 ± 50 | 0.61 |
| 17 | Number of Pumps popped on trials with Blue Balloons | 83 ± 216 | 76 ± 174 | 0.70 |
| 18 | Number of Pumps popped on trials with Orange Balloons | 76 ± 35 | 78 ± 38 | 0.56 |
| 19 | Number of Pumps popped on trials with Yellow Balloons | 73 ± 100 | 77 ± 96 | 0.63 |
| 20 | Total Blue Balloons Burst | 3.5 ± 4.25 | 3.21 ± 3.86 | 0.37 |
| 21 | Total Orange Balloons Burst | 19.6 ± 6.48 | 20.5 ± 6.78 | 0.42 |
| 22 | Total Yellow Balloons Burst | 8 ± 6.1 | 8.2 ± 6.1 | 0.55 |
| 23 | Stop Signal task | Total Successful stops | 81.8 ± 20.68 | 82.29 ± 21.37 | 0.78 |
| 24 | Trail Making test | Reaction time for  Numbers | 1496 ± 622.8 | 1501 ± 546 | 0.91 |
| 25 | Reaction time for  Letters | 4134 ± 3316 | 4067 ± 3310 | 0.80 |
| 26 | Reaction time for both  Numbers and Letters | 58107 ± 38934 | 55810 ± 35784 | 0.44 |
|
| 27 | Card Sorting Test | Correct | 2315 ± 1143 | 2283 ± 1106 | 0.73 |
| 28 | Perseverative Response | 3404 ± 4438 | 3307 ± 5244 | 0.93 |
| 29 | CORSI Block Tapping Task | Forward | -8.47 ± 100.91 | -14.51 ± 121.4 | 0.53 |
| 30 | Backward | -21.52 ± 141.5 | -27.98 ± 156.9 | 0.61 |
| 31 | Digit Span Task (DST) | Forward | -13 ± 116 | -15.7 ± 124.3 | 0.78 |
| 32 | Backward | -48.92 ± 196.3 | -78.31 ± 239.5 | 0.12 |
| 33 | Social Cognition Rating in the Indian Setting (SOCRATIS) | Faux Pas | 0.55 ± 0.26 | 0.60 ± 0.29 | 0.05 |
| 34 | First order-Theory of Mind | 0.92 ± 0.18 | 0.93 ± 0.17 | 0.73 |
| 35 | Second order-Theory of Mind | 0.46 ± 0.36 | 0.49 ± 0.39 | 0.23 |
| 36 | Demography | Age | 16.43 ± 4.37 | 15.62 ± 4.37 | 0.04 |
| 37 | Sex( | 1.29 | 1.31 | NS |
| 38 | Anthropometry | Height (in cm) | 154 ± 15.56 | 266 ± 32.0 | 0.63 |
| 39 | Weight (in Kg) | 47.03 ± 15.24 | 46.47 ± 16.57 | 0.53 |
| 40 | Body Mass Index | -0.24 ± 1.15 | -0.14 ± 1.12 | 0.26 |
| 41 | Leg Length (in cm) | 52.98 ± 6.30 | 52.44 ± 4.87 | 0.20 |
| 42 | head circumference (in cm) | 52.98 ± 6.30 | 52.44 ± 4.87 | 0.65 |
| 43 | mid-arm circumference (in cm) | 23.72 ± 4.86 | 23.50 ± 6.01 | 0.65 |

\*\*represents significant differences after Bonferroni’s correction.

NS represents non-significant differences

*Exploratory Additional Measures across two groups*

The scores of the exploratory additional behaviours that were considered in the study. The description is provided in the boxes below.

**Table 2S**- Averaged scores of CVEDA measures for the Dissimilar and the Similar-rsfMRI pattern group. Number of subjects (n) in each group is provided below the scores.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| S.No | Behavior Category | Behavior  Name | Mean ± Standard error | | *p-value* |
|  |  |  | Dissimilar rsfMRI pattern Group | Similar  rsfMRI pattern Group |
| 1 | Substance Use  (measures the amount of alcohol, tobacco and illicit drugs consumed by the participant) | Alcohol | 2.43 ± 7.69  (n = 177) | 1.41 ± 4.70  (n = 808) | 0.03 |
| 2 | Tobacco | 3.05 ± 9.33  (n = 177) | 2.09 ± 5.06  (n = 808) | 0.01 |
| 3 | Cannabis | 2.29 ± 8.07  (n = 177) | 1.81 ± 5.91  (n = 808) | 0.06 |
| 4 | Opioids | 0.30 ± 2.59  (n = 177) | 0.18 ± 1.47  (n = 808) | 0.07 |
| 5 | Inhalants | 0.85 ± 4.99  (n = 177) | 0.55 ± 3.11  (n = 808) | 0.06 |
| 7 | Prescription | 0.25 ± 2.03  (n = 177) | 0.10 ± 1.20  (n = 808) | 0.06 |
| 8 | Sleeping Pills | 0.24 ± 0.93  (n = 177) | 0.19 ± 0.91  (n = 808) | 0.16 |
| 9 | ATS | 0.05 ± 0.47  (n = 177) | 0.03 ± 0.23  (n = 808) | 0.06 |
| Cocaine | 0.33 ± 3.11  (n = 177) | 0.14 ± 1.59  (n = 808) | 0.07 |
| 10 | Strength and difficulty questionnaires  (measure of behavioural and emotional difficulties to access mental health problems) | Emotional Problem | 3.54 ± 2.53  (n = 177) | 2.84 ± 2.33  (n = 800) | 0.13 |
| 11 | Conditional Problem | 3.01 ± 2.16  (n = 177) | 1.60 ± 1.96  (n = 801) | 0.05 |
| 12 | Hyper | 3.79 ± 2.30  (n = 177) | 3.29 ± 2.20  (n = 801) | 0.17 |
| 13 | Peer | 2.35 ± 2.01  (n = 177) | 2.57 ± 1.96  (n = 801) | 0.61 |
| 14 | Prosocial | 8.53 ± 2.10  (n = 177) | 8.39 ± 2.31  (n = 799) | 0.42 |
| 15 | Total Difficulties | 12.7 ± 6.33  (n = 177) | 11.22 ± 5.99  (n = 798) | 0.10 |
| 16 | Mini-International Neuropsychiatric Interview  (short structured diagnostic interview for major psychiatric disorders). The values are represented as in ratio defined as () | Attention Deficit Hyper Activity Disorder | 0.03  (n = 106) | 0.01  (n = 515) | NS |
| 17 | Dysthymia | 0.05  (n = 176) | 0.01  (n = 804) | NS |
| 18 | Hypomanic Episode (Current) | 0.00  (n = 176) | 0.00  (n = 804) | NS |
| 19 | Hypomanic Episode (Past) | 0.02  (n = 176) | 0.00  (n = 804) | NS |
| 20 |
| 21 | Manic Episode (current) | 0.01  (n = 176) | 0.00  (n = 804) | NS |
| 22 | Manic Episode (Past) | 0.01  (n = 176) | 0.00  (n = 804) | NS |
| 23 | Agoraphobia and Panic Disorder | 0.05  (n = 176) | 0.03  (n = 804) | NS |
|
|
| 24 | Social Phobia | 0.00 (n = 172) | 0.00  (n = 804) | NS |
| 25 | Obsessive Compulsive disorder | 0.02  (n = 173) | 0.00  (n = 801) | NS |
| 26 | Post traumatic Stress Disorder | 0.00  (n = 173) | 0.00  (n = 801) | NS |
| 27 | Alcohol abuse and Dependence | 0.00  (n = 177) | 0.00  (n = 804) | NS |
| 28 | Non-alcohol psychoactive substance use disorder | 0.02  (n = 177) | 0.00  (n = 804) | NS |
|
|
| 29 | Mood Disorder | 0.01  (n = 177) | 0.00  (n = 804) | NS |
| 30 | Psychotic Disorders | ­­­­0.01  (n = 177) | 0.00  (n = 804) | NS |
| 31 | Anorexia Nervosa | 0.00  (n = 177) | 0.00  (n = 804) | NS |
| 32 | Bulimia Nervosa | 0.00  (n = 177) | 0.00  (n = 804) | NS |
| 33 | Generalised Anxiety Disorder | 0.00  (n = 177) | 0.00  (n = 804) | NS |
| 34 | Antisocial Personality Disorder | 0.00  (n = 177) | 0.00  (n = 804) | NS |
| 35 | Separation Anxiety Disorder | 0.01  (n = 106) | 0.00  (n = 515) | NS |
| 36 | Tic Disorder | 0.00  (n = 106) | 0.00  (n = 106) | NS |
| 37 | Conduct Disorder | 0.04  (n = 106) | 0.00  (n = 515) | NS |
| 38 | Oppositional Defiant Disorder | 0.03  (n = 106) | 0.00  (n = 515) | NS |
| 39 | Adjustment Disorder | 0.03  (n = 106) | 0.01  (n = 515) | NS |
| 40 | Pervasive Development Disorder | 0  (n = 106) | 0  (n = 515) | NS |
| 41 | Any Diagnosis | 0.28  (n = 177) | 0.19  (n = 803) | NS |

NS represents non-significant differences.

All behaviours (primary and exploratory) that the cVEDA team used to access the neurodevelopmental pattern were carefully selected for age-appropriateness across the children and teenagers. However, norms tailored to the Indian population, which c-VEDA cohort represents, were not available. With the cVEDA project, the team’s futuristic intentions are also to establish cultural-specific norms for the Indian demography. The absence of established norms necessitated the use of raw scores for behavioural assessment, allowing us to explore the nuanced relationships between brain patterns, cognitive performance, environmental influences and more, using a hypothesis free bottom-up approach. Since, age and sex differences between the two groups were not significant (Table 1S), regressing them also fetched similar results.

With that said, there are some interesting observations that are worth investigating in future. In Table 1S, abuse significantly differentiated the two groups. Though neglect could not survive the stringent Bonferroni’s correction, its impact on neurodevelopmental trajectory is well established. Similarly, in Table 2S, the measures in the substance use category could not pass the stringent significance test, the trend shows that the subjects in the dissimilar rsfMRI group have higher consumption. Likewise, psychiatric disorder diagnoses under the Mini-International Neuropsychiatric Interview also show a similar trend for subjects in dissimilar rsfMRI group (column 41, *Any diagnosis*).

These differences between the groups correspond to the differences in the rsfMRI features of DMN. In our previous study on ageing, behavioural differences in substance use and personality in two groups were also associated with the differences in rsfMRI features of the DMN (Kashyap et al, 2019). The present analysis strengthens our understanding that DMN, which accounts for daily habits and lifestyle, plays a vital role in neurodevelopment as well as in ageing. The interplay of several behaviours and brain mechanism underlying their imprint is complex and future research are focusing on the mental health trajectory. Since, there is a consensus towards the development of therapeutic interventions to maintain sound mental health throughout the life span (Uhlhaas et al, 2023), care needs to be taken from childhood onwards for healthy development of DMN. As environment plays a crucial role, interventional programs within families and society are necessary to immune future generations from vulnerability towards adversity.

**References**

[1] Makowski, C., Lepage, M., & Evans, A. C. (2019). Head motion: the dirty little secret of neuroimaging in psychiatry. Journal of Psychiatry and Neuroscience, 44(1), 62-68. doi: 10.1503/jpn.180022.

[2] Kashyap R, Bhattacharjee S, Yeo BT, Chen SA. Maximizing dissimilarity in resting state detects heterogeneous subtypes in healthy population associated with high substance use and problems in antisocial personality. Human brain mapping. 2019. doi: 10.1002/hbm.24873.

[3] Uhlhaas PJ, Davey CG, Mehta UM, Shah J, Torous J, Allen NB, et al. Towards a youth mental health paradigm: a perspective and roadmap. Mol Psychiatry. 2023 Aug 14;1–11. doi: 10.1038/s41380-023-02202-z.