

Exploring functional connectivity in clinical and data-driven groups of preterm and term adults

Laila Hadaya^{1,2}, František Váša³, Konstantina Dimitrakopoulou⁴, Mansoor Saqi⁴, Sukhwinder S Shergill^{5,6,7}, A David Edwards¹, Dafnis Batalle^{1,8}, Robert Leech³, and Chiara Nosarti^{1,2}

¹ Centre for the Developing Brain, Department of Perinatal Imaging and Health, King's College London, London, United Kingdom, SE1 7EH.

² Department of Child and Adolescent Psychiatry, Institute of Psychiatry Psychology and Neuroscience (IoPPN), King's College London, London, United Kingdom, SE5 8AB.

³ Department of Neuroimaging, IoPPN, King's College London, London, United Kingdom, SE5 8AB.

⁴ Translational Bioinformatics Platform, NIHR Biomedical Research Centre, Guy's and St. Thomas' NHS Foundation Trust and King's College London, London, United Kingdom, SE1 9RT.

⁵ Kent and Medway Medical School, Canterbury, United Kingdom, CT2 7FS.

⁶ Kent and Medway NHS and Social Care Partnership Trust, Maidstone, United Kingdom, ME16 9PH.

⁷ Department of Psychosis Studies, IoPPN, King's College London, London, United Kingdom, SE5 8AB.

⁸ Department of Forensic and Neurodevelopmental Sciences, IoPPN, King's College London, London, United Kingdom, SE5 8AB.

Correspondence to: Chiara Nosarti, Centre for the Developing Brain, Department of Perinatal Imaging and Health, School of Biomedical Engineering & Imaging Sciences, King's College London, First Floor South Wing, St Thomas' Hospital, London, United Kingdom SE1 7EH.

E-mail: chiara.nosarti@kcl.ac.uk

Short title: Preterm and term adult brain-behaviour

Abstract

Adults born very preterm (i.e., at <33 weeks' gestation) are more susceptible to long-lasting structural and functional brain alterations and cognitive and socio-emotional difficulties, compared to full-term controls. However, behavioural heterogeneity within very preterm and full-term individuals makes it challenging to find biomarkers of specific outcomes. To address these questions, we parsed brain-behaviour heterogeneity in participants subdivided according to their clinical birth status (very preterm vs full-term) and/or data-driven behavioural phenotype (regardless of birth status).

Participants were followed up in adulthood (median age 30 years) as part of a wider longitudinal case-control cohort study. The Network Based Statistic approach was used to identify topological components of resting state functional connectivity differentiating between i) 116 very preterm and 83 full-term adults (43% and 57% female, respectively), and ii) data-driven behavioural subgroups identified using consensus clustering (n= 156, 46% female). Age, sex, socio-economic status, and in-scanner head motion were used as confounders in all analyses. Post-hoc two-way group interactions between clinical birth status and behavioural data-driven subgrouping classification labels explored whether functional connectivity differences between very preterm and full-term adults varied according to distinct behavioural outcomes.

Very preterm compared to full-term adults had poorer scores in selective measures of cognitive and socio-emotional processing and displayed complex patterns of hyper- and hypo-connectivity in subsections of the default mode, visual, and ventral attention networks. Stratifying the study participants in terms of their behavioural profiles (irrespective of birth status), identified two data-driven subgroups: An "At-risk" subgroup, characterised by increased cognitive, mental health, and socio-emotional difficulties, displaying hypo-connectivity anchored in frontal opercular and insular regions, relative to a "Resilient" subgroup with more favourable outcomes. No significant interaction was noted between clinical birth status and behavioural data-driven subgrouping classification labels in terms of functional connectivity.

Functional connectivity differentiating between very preterm and full-term adults was dissimilar to functional connectivity differentiating between the data-driven behavioural subgroups. We speculate that functional connectivity alterations observed in very preterm relative to full-term adults may confer both risk and resilience to developing behavioural

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3 sequelae associated with very preterm birth, while the localised functional connectivity
4 alterations seen in the “At-risk” subgroup relative to the “Resilient” subgroup may underlie
5 less favourable behavioural outcomes in adulthood, irrespective of birth status.
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10 **Keywords:** preterm birth; clustering; resting state functional MRI; behaviour
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14 Introduction

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17 Very preterm birth (VPT; i.e., at <33 weeks’ gestation) occurs during a rapid stage of brain
18 development, making those born VPT vulnerable to neurological insult¹ and long-lasting
19 difficulties in attention, executive function, and socio-emotional processing.²⁻⁴ Functional
20 connectivity alterations in brain regions and networks important for cognitive and affective
21 processing have also been reported in VPT samples across the lifespan, and have been studied
22 amongst the possible biological mechanisms underlying the behavioural difficulties associated
23 with VPT birth.⁵⁻¹² It is important to highlight, however, that not only have previous studies
24 identified brain changes associated with behavioural difficulties in those born VPT, but have
25 also characterised neural adaptations which support domain-specific performance.¹³⁻¹⁷ These
26 findings, therefore, indicate that the functional reorganisation of the VPT brain has complex
27 implications for outcomes, as it may probe both risk and resilience to behavioural difficulties.
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37 Further complicating the understanding of brain-behavioural relationships in VPT
38 populations, is the fact that those born preterm tend to exhibit heterogenous behavioural
39 outcomes. Previous studies aiming to stratify this heterogeneity implemented latent profile
40 analyses using behavioural measures from both preterm and full term (FT) born children.¹⁸⁻²⁰
41 Their results indicated that while those born preterm were more likely to present with
42 psychiatric, cognitive, or socio-emotional difficulties, some preterm children displayed distinct
43 profiles characterised by fewer or no behavioural difficulties. Moreover, while FT children
44 predominantly exhibited more normo-typical behavioural profiles, some FT children displayed
45 behavioural difficulties similar to those observed in preterm children.¹⁸⁻²⁰ Together, these
46 findings indicate that VPT and FT groups exhibit both within- and between-group
47 heterogeneity, which needs to be addressed in order to develop individually tailored and
48 biologically specific interventions aimed at supporting healthy development.^{21,22} This can be
49 achieved by, firstly, implementing data-driven stratification approaches to identify distinct
50 subgroups of individuals exhibiting similar behavioural profiles, irrespective of their birth
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3 status, and secondly, by investigating brain correlates differentiating between the distinct data-
4 driven behavioural subgroups.
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8 Similarly, individuals belonging to distinct diagnostic and non-diagnostic psychiatric
9 groups also exhibit within- and between-group heterogeneity in terms of phenotypic profiles.
10 Recent studies implementing such approaches in psychiatric populations have successfully
11 identified patterns of structural and functional connectivity characterising distinct data-driven
12 behavioural subgroups irrespective of diagnostic labels.²³⁻²⁸ A small number of studies in VPT
13 children followed similar methodological approaches and investigated the underlying brain
14 changes differentiating within-group behavioural heterogeneity. Results of these studies
15 showed that early brain insult^{29,30} and structural and functional brain alterations^{20,31}
16 characterised the distinct subgroups. However, it remains to be explored whether the
17 heterogeneity in behavioural outcomes seen within and between VPT and FT born individuals
18 persists into adulthood, and if it does, whether resting state functional connectivity (rsFC)
19 changes may be associated with distinct data-driven behavioural phenotypes, irrespective of
20 gestational age at birth.
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31 Our study firstly aimed to identify long-lasting neurodevelopmental alterations
32 associated with VPT birth, by investigating differences in rsFC and behavioural outcomes
33 between VPT and FT born adults. Secondly, our study aimed to delineate behavioural
34 heterogeneity in VPT and FT born adults irrespective of gestational age at birth, by using a
35 robust data-driven consensus clustering approach to stratify participants based on behavioural
36 measures (executive function, attention, intelligence, socio-emotional processing,
37 psychopathology, and autistic traits), and to explore whether resultant data-driven behavioural
38 subgroups would exhibit differences in rsFC. Finally, to address both within- and between-
39 group heterogeneity, post-hoc analyses investigated two-way group interactions between
40 clinical (i.e., VPT vs FT birth) and behavioural (i.e., data-driven subgrouping) classification
41 labels, to explore whether rsFC pattern and behavioural measure differences between VPT and
42 FT adults, varied according to distinct behavioural outcomes.
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Materials and methods

Study design

Participants. VPT infants (i.e., born at <33 weeks of gestation) were recruited at birth from the Neonatal Unit at University College London Hospital (London, UK) between 1979 and 1985. Enrolled participants received cranial ultrasonographic imaging several times during the first week of life and weekly until discharge from hospital³² and were subsequently followed up in childhood at 1, 4 and 8 years of age,^{33,34} adolescence (15 years), early (20 years), and middle adulthood (30 years).³⁵ Age-matched controls, born at FT (37-42 weeks of gestation), were recruited from the community in middle adulthood. Exclusion criteria for the controls were any clinical complications at birth (i.e., prolonged gestation at >42 weeks, low birth weight <2500g, receiving endotracheal mechanical ventilation). Exclusion criteria for both VPT and FT participants included severe hearing and motor impairments, or history of neurological complications (i.e., meningitis, head injury, cerebral infections). For this study, we used neuroimaging and behavioural data from the middle adulthood follow-up. Please see Supplementary Figure 1 for more information about participants' selection.

Research study practices were conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the South London and Maudsley Research and Ethics Committee and the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM/12/13-10), King's College London. All participants were native English speakers. Written informed consent was obtained from all study participants and participant privacy rights were observed.

Clinical and socio-demographic details. Gestational age at birth and birth weight were collected from medical discharge notes for VPT participants. Participants born VPT were classified into three groups, according to cranial ultrasound diagnosis: no evidence of perinatal brain injury (no injury), grade I – II periventricular haemorrhage without ventricular dilation (minor injury) and grade III – IV periventricular haemorrhage with ventricular dilation (major injury).³⁶

For both VPT and FT groups, self-reported ethnicity was recorded according to the following groups: African, Afro-Caribbean, Caucasian/White, Indian Subcontinent, and Other.

Socio-economic status was defined according to participants' self-reported occupation at the time of the study and parental occupation at time of study. Occupations were categorised according to the Office of National Statistics, 1980 Standard Occupation Classification; I: Higher managerial, administrative, and professional occupations; II: Intermediate occupations, small employers, and own account workers; III: Routine and manual occupations – lower supervisory and technical and semi-routine and routine occupations.

Cognitive assessments. The following cognitive assessments were administered to measure language, executive attention, and general intelligence: Hayling Sentence Completion Test (HSCT)³⁷; Controlled Oral Word Association Test (COWAT-FAS)³⁸; four subtests from the Cambridge Neurophysiological Test Automated Battery (CANTAB) 2003 eclipse version³⁹: 1) Stockings of Cambridge (SOC), 2) Intra-Extra Dimensional Set Shift (IED), 3) Paired Associates Learning (PAL), and 4) Motor Screening Task (MOT); the Trail Making Task – B (TMT-B)⁴⁰; Continuous Performance Test – 2nd edition (CPT)⁴¹; and Wechsler Abbreviated Scale of Intelligence (WASI)⁴². Specific task descriptions are detailed in Supplementary Table 1.

Psychiatric and behavioural assessments. General psychopathology was measured using the Comprehensive Assessment of At-Risk Mental States (CAARMS)⁴³, a semi-structured clinical interview which measures aspects of psychopathology relating to mania, depression, suicidality and self-harm, mood swings/lability, anxiety, obsessive compulsive disorder symptoms, dissociative symptoms, and impaired tolerance to normal stress; scores on the general psychopathology subscale were used in our analyses. The self-administered General Health Questionnaire (GHQ-12)⁴⁴ was used to measure general well-being, Peters Delusion Inventory (PDI)⁴⁵ to measure delusional ideation traits, Autism Quotient (AQ-10)^{46,47} to measure autism traits (i.e., social interaction, communication, attention switching, attention to detail, and imagination), Social Adjustment Scale (SAS)⁴⁸ to measure participants' satisfaction with their social situation, and Role Functioning Scale (RFS)⁴⁹ to measure individuals' ability to function in their daily life. The Emotion recognition task (ERT)⁵⁰ was administered to measure participants' ability to recognise expressed emotions (happiness, sadness, surprise, anger, disgust and fear), as described in our previous work.⁸

Structural and functional magnetic resonance imaging (MRI) acquisition. MRI data were acquired at the Maudsley Hospital, London, using a 3 Tesla Signa MR scanner (General Electric Healthcare). Structural fast spoiled gradient-echo (FSPGR) pulse sequence T1-

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3 weighted images were collected using the following sequence parameters: TR=7.1 ms, TE=2.8
4 ms, matrix=256x256, voxel size=1.1 mm isotropic. Gradient echo EPI resting state functional
5 MRI data were collected while participants stared at a central cross on a screen for 8 minutes
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7 32 s, using the following parameters 256 volumes, TR=2000 ms, TE=30 ms, flip angle=75
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9 degrees, matrix=64x64, 37 non-contiguous slices of 2.4 mm thickness, 1.1 mm interslice gap,
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11 and 3.4 mm in-plane resolution.
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14 15 **MRI data pre-processing**

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17 Resting state functional MRI data pre-processing was performed using fMRIPrep
18 20.1.1, RRID:SCR_016216,⁵¹ which is based on Nipype 1.5.0, RRID:SCR_002502.⁵² In
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20 summary, steps included skull stripping, slice-time correction, co-registration to the T1w
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22 reference image using boundary-based registration⁵³ and head motion estimation (i.e., global
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24 signal and six motion parameters: three translation and three rotation parameters). The
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26 complete pre-processing protocol is detailed in the Supplementary Material.
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29 After pre-processing, data were de-noised by regressing out estimated motion
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31 confounders (i.e., global signal and six motion parameters: three translation and three rotation
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33 parameters) using the FMRIB Software Library (FSL) *fsl_regfilt* command.⁵⁴ A band-pass
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35 filter (0.01 – 0.1 Hz) was applied to the data using the AFNI software *3dBandpass* command.⁵⁵
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37 Participants were excluded if they exhibited excessive in-scanner head motion (i.e., mean
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39 frame-wise displacement (FD) exceeding 0.4mm or a maximum FD exceeding 4mm) or had
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41 functional MRI scans showing poor alignment with anatomical data. Sample sizes and
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43 participant exclusions are summarised in a flowchart in Supplementary Figure 1.
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46 47 **Brain parcellation and rsFC estimation**

48 Resting state functional MRI data were parcellated into bilaterally symmetric cortical
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50 regions using the Human Connectome Project Multi-Modal Parcellation; HCP-MMP (v1)
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52 atlas⁵⁶ and bilateral subcortical FreeSurfer regions.⁵⁷ The two bilateral hippocampal regions
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54 from the HCP-MMP atlas were excluded as these regions were included as part of the
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56 FreeSurfer subcortical segmentation, resulting in a total of 374 regions included in our analyses
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58 (i.e., 358 HCP-MMP atlas bilateral cortical regions and 16 FreeSurfer bilateral subcortical
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60 regions).

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3 An average of the functional MRI blood oxygen level-dependent (BOLD) signal time
4 series across all voxels in each parcellation was used to estimate the regional time series for
5 each of the 374 brain regions. For each participant, rsFC matrices were calculated using
6 Pearson's correlations between pairs of all 374 regional time series. A threshold of 0.2 was
7 used to eliminate weak correlations (i.e., weights of edges with $r \geq 0.2$ were retained)
8 potentially corresponding to spurious connections.⁵⁸⁻⁶⁰ This was applied independently for
9 each participant, followed by a Fisher Z-transformation.

16 17 **Consensus clustering**

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19 To partition participants (both VPT and FT; n=156) into data-driven behavioural
20 subgroups, a consensus clustering pipeline (Fig. 1) was implemented using the following 13
21 behavioural measures as input features: COWAT-FAS mean total words produced, SOC total
22 number of problems solved, IED total errors adjusted, MOT mean reaction time, TMT-B time
23 elapsed, CPT total reaction time, full-scale IQ, total PDI score, total AQ10 score, CAARMS
24 total general psychopathology score, total GHQ score, ERT total number of correct responses
25 and total SAS score (see Supplementary Material for data pre-processing and feature selection
26 procedures).

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28 Each variable was first standardised to have a mean = 0 and standard deviation = 1, and
29 an Euclidean distance matrix of the input data was calculated. A similarity matrix (network)
30 was then calculated from the distance matrix, using the *affinityMatrix* function (SNFtool R
31 package),⁶¹ which utilises two hyperparameters: neighbourhood size (K) and alpha (edge
32 weighting parameter) that help increase the signal to noise ratio and in turn improve result
33 validity and reliability. K corresponds to the number of surrounding nodes to consider for each
34 node in the similarity network and alpha determines a threshold for the strength of the edges in
35 the similarity network (i.e., pairwise similarity between nodes within the sample). Greater K
36 values result in more dense similarity networks and smaller values result in more sparse
37 similarity networks, while greater alpha values result in weaker edges being retained and
38 smaller alpha values result in similarity networks which retain edges with higher similarity.
39 Thirty different K-alpha combinations were used to generate thirty similarity networks based
40 on the following values: K = 10, 15, 20, 25, 30 and alpha = 0.3, 0.4, 0.5, 0.6, 0.7, 0.8. These
41 values lie within the ranges recommended in the SNFtool package: 10–30 for K and 0.3–0.8
42 alpha.⁶¹ Each of the resultant thirty similarity networks was successively inputted into the
43 consensus clustering algorithm (*ConsensusClusterPlus* function, *ConsensusClusterPlus* R

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3 package)⁶² which performs agglomerative hierarchical clustering following a nested
4 bootstrapping (n=1000) spectral clustering for each of the thirty similarity networks. From the
5 thirty resultant clustering outputs, the solution with the highest average silhouette width score
6 was retained.
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11 In order to improve the generalisability of our solution and avoid overfitting of
12 hyperparameter selection, the steps described in the above paragraph were repeated 1,000 times
13 where a randomised selection of 80% of the sample was used each time. The final resultant
14 1,000 clustering outputs were then fed into a hierarchical clustering function
15 (*consensus_combine*, DiceR package),⁶³ to output a final consensus clustering result based on
16 the consensus matrix.
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22 To determine the optimal number of clusters (C), Eigengap and Rotation Cost metrics
23 were firstly used to estimate the best and second-best number of clusters
24 (*estimateNumberOfClustersGivenGraph* function SNFtool R package)⁶¹ for each of the thirty
25 K-alpha combinations, identifying C=2, C=3, and C=5 as the top three clustering solutions. We
26 then ran the described consensus clustering pipeline three separate times, once for each of these
27 solutions (C=2, C=3, and C=5), and subsequently calculated consensus matrices and silhouette
28 scores for each cluster solution. Resultant consensus matrix and silhouette score outputs
29 suggested an optimal number of clusters of C=2 (Supplementary Figure 2); therefore, we
30 evaluate subgroups obtained from the C=2 solution.
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38 The consensus clustering pipeline implemented here is adapted from the integrative
39 clustering method used in our previous work,³¹ code: <https://github.com/lailahadaya/preterm-ExecuteSNF.C>, where we do not apply the data-integration step in the current study.
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45 **Statistical analyses**

46 **Evaluation of clinical, socio-demographic, and behavioural profiles**

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48 The non-parametric Wilcox rank sum test was used for continuous variables and Chi-
49 squared or Fischer's Exact tests for categorical variables. Effect sizes were calculated using
50 Wilcoxon Glass Rank Biserial Correlation for continuous variables and Cramer's V (V) for
51 categorical variables. False Discovery Rate (FDR) was used to account for multiple comparison
52 testing.⁶⁴ Sensitivity analyses using non-parametric permutation testing (5000 permutations)
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3 adjusted for age, sex, and socio-economic status.⁶⁵ P-values < 0.05 were considered to be
4 statistically significant.
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8 **Between-group differences in rsFC at a topological network-level**

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10 The Network Based Statistic (NBS), a cluster-based statistics approach, was applied.⁶⁶ NBS
11 implements the following steps: 1) mass-univariate testing with a suitable statistical test of
12 interest on all possible connections (i.e., edges), 2) next, only edges with p-values below a pre-
13 defined threshold (p-NBS-Threshold) are maintained, 3) retained suprathreshold edges are then
14 used to identify topologically connected structures (referred to as NBS ‘components’) present
15 amongst the collection of suprathreshold edges using breadth-first search,⁶⁷ and finally, 4)
16 permutation testing is used to assign a Family Wise Error Rate corrected p-value (p-FWER)
17 for each identified component, based on the component’s strength. NBS testing is derived from
18 traditional cluster-based thresholding of statistical maps; however, rather than generating
19 clusters of voxels with spatial proximity in physical space, NBS can be applied to graph-like
20 structures to generate clusters with interconnected edges in topological space.^{66,68} An
21 advantage of using NBS, compared to an approach that controls for FWER at an edgewise basis
22 (such as False-Discovery Rate), is that it can provide increased statistical power by detecting
23 the effect of interest in a collection of connections which are collectively contributing to the
24 effect of interest as opposed to uniquely contributing to the effect on an individual edgewise-
25 level.
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40 Selecting a threshold in NBS (described in step 2 above) is a relatively arbitrary choice,
41 which can be determined by experimenting with a selection of conservative and stringent
42 thresholds.⁶⁶ We ran NBS testing at three different p-value thresholds (i.e., p-NBS-Threshold
43 = 0.05, 0.01, and 0.001) to identify relevant suprathreshold edges to be grouped into NBS
44 components for further analysis. We implemented NBS testing with 1000 permutations using
45 the NBR R package *nbr_lm* function (NBR).⁶⁹ Statistical models tested included the following
46 covariates: mean FD (as a measure of in-scanner head motion), sex, age, and socio-economic
47 status. The same sets of methods were implemented to identify differences in rsFC between 1)
48 VPT and FT individuals and 2) data-driven behavioural subgroups.
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55 NBS generates two resultant outputs: 1) component strength or intensity – i.e., the sum
56 of test statistic (T-statistic) values from all edges within the significant component, and 2)
57 component size or extent – i.e., the number of connections comprising the significant
58 component. We also calculated the number of connections belonging to each node within the
59 component.
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3 component as a proportion of the total number of possible edges within that component and
4 presented results graphically using the ggseg3d R package.⁷⁰ To measure within and between
5 network connectivity, we labelled nodes according to seven previously defined intrinsic
6 connectivity networks (i.e., visual, somatomotor, dorsal attention, ventral attention (VAN),
7 limbic, frontoparietal, and default mode (DMN) networks)⁷¹ and an eighth network comprised
8 of 16 subcortical regions⁷² and calculated connectivity proportion and strength; code accessible
9 at:

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12 https://github.com/frantisekvasa/functional_network_development/blob/master/nspn_fmri.R.
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15 16 17 18 **Post-hoc exploratory analyses** 19

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21 We estimated the extent of nodal and edgewise overlap between the NBS components
22 characterising clinical (i.e., VPT vs FT birth) and data-driven behavioural subgrouping
23 classifications using the Sørensen-Dice similarity coefficient, which is calculated as the ratio
24 of two times the number of overlapping features between two sets, over the total number of
25 features present across both sets,⁷³ with values ranging between 0 and 1. The hypergeometric
26 cumulative density function was used to assess the significance of the overlapping edges
27 between the two NBS components as described in.⁷⁴
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34 To address both within- and between-group heterogeneity, post-hoc exploratory NBS
35 analyses investigated whether differences in rsFC between VPT and FT clinical groups varied
36 according to distinct behavioural outcome subgrouping, using two-way group interactions
37 between clinical and data-driven behavioural classification labels. Two-way group interaction
38 analyses were also used to investigate whether differences in behavioural outcomes between
39 VPT and FT clinical groups varied according to behavioural outcome subgrouping.
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45 We also investigated differences in early clinical risk (i.e., gestational age at birth, birth
46 weight, and perinatal brain injury) and socio-demographic measures between VPT adults
47 belonging to the distinct data-driven behavioural subgroups, and in socio-demographic
48 measures between FT adults in the distinct data-driven subgroups.
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Results

VPT and FT groups

The socio-demographic and clinical profiles of VPT and FT adults are summarised in Table 1 and their behavioural outcomes in Table 2 and Fig. 2A. In summary, adults born VPT had significantly lower full-scale IQ (WASI), attention set shifting (CANTAB-IED), and emotion recognition (ERT) scores than adults born (p<0.05) FT. Head motion during functional MRI acquisition was greater in the VPT (median FD = 0.15mm, range=0.07 – 0.40mm) than the FT group (median FD=0.12mm, range=0.05 – 0.35mm; p<0.001). Supplementary analyses show that VPT adults excluded from analyses (n=37) for reasons described in Supplementary Figure 1, had relatively poorer cognitive and socio-emotional scores compared to those VPT adults included in the analyses (n=116) (Supplementary Table 2).

Data-driven behavioural subgroups

The socio-demographic and clinical profiles of VPT and FT study participants used for the data-driven consensus clustering analyses are summarised in Table 3. Two data-driven behavioural subgroups were identified and labelled as ‘At-risk’ and ‘Resilient’, based on their observed phenotypic profiles (Table 4; Fig. 2B).

In summary, the At-risk subgroup had significantly less optimal executive function and attention scores probing spatial planning, attentional set shifting, visuo-motor coordination, comprehension abilities, sustained attention and response inhibition (CANTAB – SOC, MOT and IED, the TMT-B, and CPT), compared to the Resilient subgroup (p<0.05). The At-risk subgroup also had significantly less optimal social adjustment, mental wellbeing, and psychiatric scores (PDI, CAARMS, GHQ, and SAS), and significantly increased autistic traits (AQ-10 scores), compared to the Resilient subgroup (p<0.05). The two subgroups showed no differences in full-scale IQ (WASI), emotion recognition (ERT), or phonemic verbal fluency (COWAT). However, the At-risk subgroup had a significantly higher proportion of individuals with lower own socio-economic status compared to the Resilient subgroup (p<0.05). Parental socio-economic status did not differ between the subgroups.

52% of the VPT adults in our sample clustered into the At-risk subgroup, and the remaining 48% into the Resilient subgroup (Fig. 3). Upon examining VPT adults only, there were no significant differences between the At-risk and Resilient subgroups in terms of

perinatal clinical measures (i.e., gestational age, birth weight, or perinatal brain injury) (Supplementary Table 3; Supplementary Figure 3). In terms of parental socio-economic status, there were no differences between At-risk and Resilient subgroups within VPT or FT adults (Supplementary Table 3 and Supplementary Table 4, respectively). As for participants' own socio-economic status, only those born VPT displayed significant differences between the data-driven behavioural subgroups, where more VPT individuals with higher managerial, administrative, and professional occupations belonged the Resilient subgroup compared to the At-Risk subgroup (Supplementary Table 3) ($p < 0.05$). However, socio-economic status for those born FT did not differ significantly between the two data-driven subgroups (Supplementary Table 4).

Post-hoc analyses investigating whether differences in behavioural outcomes between VPT and FT clinical groups varied according to behavioural outcome subgrouping report no significant two-way group interaction effects (Supplementary Table 5).

Between-group differences in rsFC

We report NBS analyses using p-NBS-Threshold values powered to detect a significant effect, whilst also reducing component size (i.e., not $p = 0.05$) (Supplementary Table 6). Main results reported here are from one-tailed NBS analyses using p-NBS-Threshold = 0.01, and additional sensitivity analyses investigating rsFC using a more stringent threshold (p-NBS-Threshold = 0.001) are reported in Supplementary Material (Supplementary Figure 4).

VPT < FT. NBS results showed weaker rsFC in the VPT group compared to the FT group (i.e., VPT < FT) in one component comprising 360 nodes (i.e., 96.25% of all regions) and 1467 edges (i.e., 2.10% of the 69,751 possible connections), with a component strength of 616.04 (p-FWER value = 0.007). Regions included in this component were widespread across the brain (Fig. 4A; Supplementary Table 7). Nodes with the highest number of connections within the component (i.e., component 'hub' regions) were predominantly localised to superior temporal gyrus, inferior and superior parietal cortex, inferior frontal, orbitofrontal, anterior cingulate and medial prefrontal cortex, inferior premotor, a lateral occipital/posterior temporal visual area, dorsolateral prefrontal cortex, medial and lateral temporal, and posterior cingulate cortex. Component within- and between-network connectivity was highest in the DMN (Fig. 5A).

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VPT > FT. NBS results also showed greater rsFC in the VPT group compared to the FT group (i.e., VPT > FT) in one component comprising 340 nodes (i.e., 90.91% of regions), 962 edges (i.e., 1.37% of possible connections) and component strength of 358.03 (p-FWER value < 0.001). ‘Hub’ regions within this component were less widespread across the brain and localised within posterior opercular cortex, posterior cingulate cortex, inferior parietal cortex, right orbitofrontal cortex, bilateral anterior cingulate and medial prefrontal cortex, superior temporal gyrus (auditory association cortex), dorsolateral prefrontal cortex, right lateral temporal cortex, right temporo-parietal-occipital junction, and medial superior parietal cortex (Fig. 4A; Supplementary Table 8). The highest number of connections found in the component were within the DMN itself, followed by a moderate number of widespread connections in the VAN, and especially between the VAN and the visual network.

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A total of 326 nodes (i.e., 87.17% of regions) were present in both VPT < FT and VPT > FT components; however, the sets of edges connecting nodes within each component were mutually exclusive with no overlapping edges.

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At-Risk < Resilient. Contrasts testing for lower rsFC in the At-risk compared to the Resilient subgroup identified one significant NBS component with 337 nodes (i.e., 90.11% of regions), 832 edges (i.e., 1.19% of possible connections) and a strength sum of 309.04 (p-FWER = 0.019). Hub regions with the highest number of connections within the component were predominantly located in insular, frontal opercular, and posterior opercular cortex (Fig. 4B; Supplementary Table 9). Other hub regions were found in the left inferior frontal cortex, lateral temporal cortex, right temporo-occipital visual area, left temporo-parieto-occipital junction, anterior cingulate, medial prefrontal cortex, left supplementary motor area, primary somatosensory cortex, and the superior temporal sulcus (auditory association cortex) (Fig. 4B; Supplementary Table 9). Component within- and between-network connectivity were most pronounced between the VAN and somatomotor networks, and within the VAN (Fig. 5B).

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At-Risk > Resilient. No significant NBS components were detected when testing for higher rsFC in the At-risk compared to the Resilient subgroup.

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Confirming the robustness of the observed effects from analyses using a p-NBS-threshold of 0.01, sensitivity NBS analyses using a more stringent p-NBS-threshold of 0.001 reported significant components with greater sparsity (Supplementary Table 10), but largely similar rsFC patterns (Fig. 4; Fig. 5Av; Fig. 5Bv).

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Post-hoc analyses investigating the interaction between clinical (VPT vs FT) groups and data-driven behavioural subgroups (At-risk vs Resilient) on rsFC did not identify significant components ($p\text{-FWER} > 0.05$) at any $p\text{-NBS-Threshold}$ examined (0.05, 0.01, and 0.001). Similarity index calculations indicated that the At-risk < Resilient component had a high number of nodes, which were also part of the VPT < FT component ($n=325$; Sørensen-Dice = 0.93) and the VPT > FT component ($n=304$; Sørensen-Dice = 0.90), but very few edges overlapped with either clinical component; $n=9$ edges (Sørensen-Dice = 0.01) and $n=22$ edges (Sørensen-Dice = 0.03), respectively. Hypergeometric cumulative density function calculations indicate no statistical significance of the observed overlapping edges ($p\text{-value} = 0.811$).

Discussion

In this study, we compared rsFC between groups of adults stratified in terms of (i) their clinical characteristics (i.e., VPT and FT birth) as well as (ii) their behavioural profiles identified using data-driven consensus clustering, regardless of their gestational age at birth. In VPT compared to FT adults, we identified complex preterm-specific patterns of both increased and decreased intrinsic rsFC predominately characterised by hypo-connectivity between the DMN and other networks examined and hyper-connectivity within the DMN and between the VAN and the visual network. When VPT and FT born adults were stratified in terms of their data-driven behavioural profiles, irrespective of gestational age at birth, we identified an ‘At-risk’ subgroup with more behavioural difficulties and reduced rsFC anchored in frontal opercular and insular areas of the VAN, relative to a ‘Resilient’ subgroup with more favourable behavioural outcomes.

In summary, our results indicate that there are complex and widespread long-lasting preterm-specific rsFC alterations, which we speculate may confer both risk and resilience to the behavioural sequelae associated with VPT birth. That is, while these rsFC alterations may partly explain the behavioural difficulties specific to those born VPT in cognitive and socio-emotional processing observed here, they may also aid the preservation of optimal outcomes in other behavioural domains where no between-group differences were noted (e.g., psychiatric difficulties, sustained attention, planning or phonemic verbal fluency). On the other hand, localised functional hypo-connectivity anchored in insular and frontal opercular regions

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3 observed in our study may characterise participants with unfavourable compared to favourable
4 cognitive and behavioural outcomes, irrespective of birth status.
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8 **Differences in rsFC and behavioural outcomes between VPT and FT born** 9 **adults**

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12 We identified complex patterns of both hypo- and hyper-connectivity predominantly
13 located in the DMN, VAN, and visual networks in VPT compared to FT participants. Such
14 rsFC alterations are evident in adulthood and may represent the neurobiological architecture
15 underlying the attentional, cognitive, and socio-emotional processing difficulties associated
16 with VPT birth, commonly referred to as the “preterm behavioural phenotype”.³ However, in
17 our cohort, VPT relative to FT born adults only differed in selected dimensions that have been
18 studied as part of the “preterm behavioural phenotype”; they had lower full-scale IQ,
19 difficulties in rule learning, attentional set shifting abilities (measured by the CANTAB IED),
20 and emotion recognition.
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30 VPT adults, compared to controls, displayed functional hypo-connectivity between the
31 DMN and the visual, somatomotor, dorsal attention, limbic and frontoparietal networks, as well
32 as hyper-connectivity within the DMN itself. In line with our findings, patterns of both hyper-
33 and hypo-connectivity in the DMN have been previously reported in VPT born children and
34 adults,^{5,75-77} suggesting that functional DMN connectivity alterations may be characteristic of
35 VPT samples. Functional DMN connectivity emerges during the third trimester of gestation, a
36 critical period of brain development during which VPT infants are born, and previous studies
37 have reported structural and functional brain alterations at term-equivalent age in regions
38 belonging to the DMN.⁷⁸⁻⁸² Extending beyond preterm populations, functional alterations in
39 the DMN have been described in several psychiatric conditions, including schizophrenia,
40 anxiety, and mood disorders,^{83,84} suggesting that the DMN rsFC alterations observed in VPT
41 individuals may represent neurobiological changes which could contribute to the behavioural
42 difficulties associated with VPT birth.
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52 On the other hand, alterations in DMN rsFC have also been studied as adaptive neural
53 mechanisms; for instance, maintaining attentional capture (i.e., less distractibility) in male
54 veterans.⁸⁵ Such findings suggest that functional reorganisation of the DMN may also reflect
55 compensatory biological alterations supporting selective cognitive and behavioural processing
56 in VPT individuals; in this context referring to the behavioural outcomes where no between-
57 group differences were noted in our study sample, including spatial planning (CANTAB –
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3 SOC), coordination (MOT), cognitive flexibility (TMT-B), phonemic verbal fluency
4 (COWAT), sustained attention (CPT), social adaptation (SAS), prodromal symptoms (PDI),
5 autism traits (AQ10) and general psychopathology (CAARMS and GHQ). This finding
6 emphasises the notion that complex neurobiological alterations following VPT birth may
7 confer both risk and resilience to the long-term consequences of VPT birth. Further supporting
8 this point, we also identified patterns of hyper-connectivity in the VPT relative to the FT group
9 in the VAN, a “circuit-breaker” network which disengages during tasks requiring focused
10 attention and activates to redirect attention towards external task-irrelevant stimuli.^{86,87}
11 Notably, the highest proportion of connections were between the VAN and the visual network,
12 which may reflect adaptive functional reorganisation in the VPT group. In a previous study,
13 stronger rsFC changes in visual and attention networks were associated with fewer attention
14 deficits in visual short-term memory storage in VPT relative to FT adults.¹⁴ Another study
15 found that attention processing was selectively supported by VAN and visual network
16 connectivity in VPT born children, and by dorsal attention, frontoparietal, and cingulo-
17 opercular network connectivity in FT controls.⁷⁷ The authors argued that VPT children may
18 have a greater reliance on visually stimulated “bottom-up” neural processes to maintain
19 attention mechanisms, which is in line with their previous findings showing poorer attention
20 abilities in VPT children with reduced volumes in regions of the visual network.⁸⁸

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22 We also identified that component ‘hub’ regions (i.e., those with a high percentage of
23 connections within the component) with higher rsFC in the VPT group relative to the FT group,
24 were localised to brain regions previously identified as nodes of a ‘rich-club’ network (i.e., the
25 sub-network of highly connected brain regions which are also highly connected to one another),
26 important for efficient integration and transfer of information between systems.^{89,90} We
27 previously reported stronger rich-club network structural connectivity and weaker peripheral
28 connectivity in an overlapping sample of VPT adults compared to FT controls, and argued that
29 increased resources in the VPT brain may be preferentially allocated to the rich-club network
30 in order to maintain efficient information exchange across the brain.⁹¹ Furthermore,
31 overlapping areas in higher order association cortices seem to have the greatest levels of inter-
32 individual variability in adulthood,⁹² and preterm neonates at term.⁹³ They have also been
33 reported to demonstrate the greatest increase in variability from infancy to adulthood in preterm
34 born individuals,⁹³ suggesting long-lasting opportunity for environmental post-natal factors to
35 contribute towards the development of adaptive neural mechanisms in the VPT adult.

Differences in rsFC and behavioural outcomes between data-driven behavioural subgroups

Considering the neurodevelopmental heterogeneity exhibited within and between those born VPT and FT, it remains to be established whether we can use rsFC to characterise the behavioural difficulties observed in VPT individuals.^{2,94} Aiming to address this question, we stratified VPT and FT adults into data-driven behavioural subgroups and investigated specific rsFC alterations which may differentiate between them. We identified two data-driven behavioural subgroups, irrespective of birth status (VPT and FT): an 'At-risk' subgroup with more executive function, attention, socio-emotional, and psychiatric difficulties, compared to a 'Resilient' subgroup, with more favourable behavioural outcomes. Notably, the behavioural differences observed between data-driven subgroups were more pronounced than those observed between VPT and FT adults.

We also identified underlying rsFC differences characterising the distinct data-driven behavioural subgroups, where the At-risk, compared to the Resilient subgroup, displayed hypo-connectivity within the VAN and between the VAN and the somatomotor network. Specifically, the predominant connectivity patterns forming this component were anchored in frontal opercular and insular regions of the brain, which play an integral role in detecting bottom-up salient information from the environment and switching between networks to produce appropriate cognitive control, socio-emotional, and interoceptive somatomotor responses.⁹⁵⁻¹⁰⁰ Our findings here are in line with previous studies showing structural and functional alterations in insular and opercular regions in adults experiencing mental health difficulties^{101,102} and executive dysfunction.¹⁰³ Furthermore, studies investigating rsFC across multiple psychiatric groups identified transdiagnostic patterns of hypo-connectivity in lower-order networks, such as the somatomotor network, as well as higher order networks, such as the VAN.^{104,105} The rsFC patterns identified here characterised data-driven behavioural subgroups irrespective of gestational age at birth (VPT and FT), indicating that these specific neural mechanisms may represent biomarkers of behavioural outcomes in the general population which are not unique to VPT individuals. We also found no significant interaction effects between birth group (VPT vs FT) and data-driven behavioural subgroups (At-risk vs Resilient) on rsFC and very little overlap in rsFC between the clinical and behavioural components identified by NBS, which may further support our speculation that the differences in rsFC between the data-driven subgroups may be characterising behavioural outcomes independently of gestational age at birth. However, future studies with larger samples, and

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3 hence greater statistical power, may further investigate the possible influence of VPT (vs FT)
4 birth on the relationship between rsFC alterations and behavioural outcomes.
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8 Our post-hoc analyses aimed to explore whether specific enriching factors, or lack of
9 certain social or clinical risk factors, protected the VPT adults belonging to the Resilient
10 subgroup from developing an At-risk behavioural profile. In contrast to previous studies in
11 VPT children, we found that perinatal clinical risk was not higher in VPT adults who belonged
12 to an At-risk (vs Resilient) subgroup.^{31,106} Social risk, on the other hand, may be specifically
13 related to the difficulties observed in the VPT At-risk subgroup, which contained more VPT
14 adults from more socially disadvantaged backgrounds compared to the Resilient subgroup,
15 while this relationship was not observed in FT adults. These findings as well as previous studies
16 in children^{20,30,31,107} could be interpreted within a “differential susceptibility” framework,
17 which posits that vulnerable individuals (e.g., those born VPT) are particularly sensitive to
18 environmental influences, where negative or positive factors (such as social (dis)advantage)
19 can promote either worse or more optimal outcomes, respectively.¹⁰⁸ Therefore, VPT adults in
20 the At-risk subgroup may have experienced a “double-hit” of being born VPT as well as being
21 socio-economically disadvantaged. Nonetheless, it is worth noting, that socio-economic status
22 in our sample only partially explained behavioural outcomes, as our main behavioural and rsFC
23 results remained significant after adjusting for this covariate. It is therefore plausible that
24 additional unmeasured environmental or hereditary factors (e.g., parental mental health or
25 cognitively stimulating home environment)^{20,31,107} may have contributed to the behavioural
26 outcomes observed in the distinct subgroups.
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41 This study has several strengths, which include the use of a large sample of both VPT and
42 FT born controls, the implementation of rigorous consensus clustering methods to obtain data-
43 driven behavioural subgroups, as well as the use of fMRIPrep, a robust automated resting state
44 functional MRI pre-processing pipeline which promotes pre-processing transparency and aims
45 to alleviate hurdles related to reproducibility in functional MRI analyses.^{51,109} We also
46 acknowledge several limitations to our study. For instance, we recognise that the choice of 0.2
47 as the threshold to eliminate weak connections is relatively arbitrary. While some argue that
48 thresholding has benefits in reducing the number of spurious connections assessed and hence
49 enhances biological plausibility,⁶⁰ others report no practical benefits from thresholding.¹¹⁰
50 Furthermore, after excluding participants with excessive head motion, behavioural outliers,
51 missing data, or poor alignment of functional MRI data, supplementary analyses showed that
52 the subsample of VPT adults used in our analyses had relatively better cognitive and socio-
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3 emotional processing outcomes in comparison to VPT adults excluded from the analyses. This
4 may limit the generalisability of our results to cohorts of low-risk VPT adults with relatively
5 favourable behavioural outcomes. It may also explain why our two data-driven behavioural
6 subgroups have similar proportions of VPT and FT born individuals, which is not in line with
7 previous studies in children that have reported higher ratios of VPT to FT individuals belonging
8 to At-risk subgroups and lower ratios to Resilient subgroups.^{18,20} On the other hand, our results
9 may be reflective of the increased rates of mental health difficulties with increasing age, which
10 may not yet be apparent in childhood.^{111,112} Future studies with more representative samples of
11 VPT adults could help elucidate these potentially inconsistent findings. Furthermore, in our
12 analyses we did not account for structural brain changes which we have previously reported
13 between an overlapping sample of VPT and FT individuals³⁵ This represents a limitation of the
14 current study as brain anatomy necessarily constrains function¹¹³ and early brain injury has
15 been associated with alterations of functional (and structural) connectivity in preterm
16 samples.¹¹⁴ Another limitation is the lack of availability of information about postnatal
17 treatment and course and co-morbidities such as broncho-pulmonary dysplasia, that are known
18 to be associated with both behavioural outcomes and alterations in brain connectivity.¹¹⁵⁻¹¹⁸
19 Another possible limitation is that we did not include known risk factors (such as socio-
20 economic status, parenting or clinical measures) in the clustering model, which may have
21 increased the difficulty in identifying nuanced subgroups exhibiting ‘equifinal’ trajectories
22 (i.e., those with similar behavioural outcomes but distinct underlying risk factors).^{31,119} The
23 heterogeneity in underlying risk factors exhibited by those born VPT could also potentially
24 hinder the ability to detect group differences between VPT and FT individuals. However, to
25 our knowledge, this is the first study to parse behavioural heterogeneity in VPT adults;
26 therefore, we decided to follow an approach similar to those implemented in the vast majority
27 of studies in VPT children, where individual-level behavioural variables were included as
28 inputs to the clustering model and risk factors were explored post-hoc.^{18-20,29,30,106,120}

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49 In summary, this study shows that there are complex patterns of rsFC alterations which are
50 specifically associated with VPT birth in adult life. We speculate that these alterations may
51 reflect neural adaptations conferring both risk and resilience to the long-term sequelae of VPT
52 birth. We also identify distinct rsFC alterations in insular and frontal opercular regions in a
53 data-driven At-risk relative to a Resilient behavioural subgroup, irrespective of birth status
54 (VPT vs FT), indicating that these neurobiological changes may reflect biomarkers of
55 behavioural outcomes in the general population that are not unique to those born VPT.
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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain Communications* online.

Data availability

Access to data supporting the published work can be made available upon request from the corresponding author. Code used to label nodes according to intrinsic network membership is accessible here:

https://github.com/frantisekvasa/functional_network_development/blob/master/nspn_fmri.R
and code used to run consensus clustering pipelines is adapted from code accessible here:
<https://github.com/lailahadaya/preterm-ExecuteSNF.CC>.

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Figure legends

Figure 1. Consensus clustering pipeline followed.

Figure 2. Radar plots showing differences in behavioural profiles between (A) VPT and FT adults and (B) At-risk and Resilient data-driven behavioural subgroups. Z-scores were computed for each group and plotted accordingly. For visual illustrative purposes, values for scales indicating poorer outcomes were reversed, so that larger Z-scores here indicate generally more optimal outcomes. *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.001$. Statistical analyses investigating differences between groups were performed using the non-parametric Wilcoxon rank sum test. Abbreviations: AQ10 = Autism Quotient; CANTAB = Cambridge Neurophysiological Test Automated Battery; CAARMS = Comprehensive Assessment of At-Risk Mental States; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; ERT = Emotion Recognition Task; FT = full-term; GHQ = General Health Questionnaire; IED = Intra-Extra Dimensional Set Shift; MOT = Motor Screening Task; PDI = Peters Delusion Inventory; SAS = Social Adjustment Scale; SOC = Stockings of Cambridge; TMT-B = Trail Making Task B; VPT = very preterm; WASI = Wechsler Abbreviated Scale of Intelligence.

Figure 3. Alluvial plot showing VPT (in blue) and FT (in grey) adults clustering into the At-risk and Resilient data-driven behavioural subgroups.

Figure 4. Percentage of edges connected to each region (i.e., node) within the significant NBS components for (A) VPT vs FT groups and (B) At-risk vs Resilient behavioural subgroups. Darker colours (blue) denote higher percentages of edges and lighter colours (yellow) denote lower percentages, with areas marked in grey indicating regions that are not forming part of the NBS component. Statistical analyses investigating rsFC differences between groups were performed using NBS, which performed mass-univariate linear models (correcting for covariates age, sex, in-scanner head motion, and socio-economic status) on an edgewise level, with the following parameters: p-NBS-Threshold = 0.01 and 1000 permutations.

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3 **Figure 5. Within- and between-network connectivity of the significant NBS components**
4 **in (A) VPT vs FT groups and (B) At-risk vs Resilient behavioural subgroups.** Results from
5 main NBS analyses using a p-NBS-threshold of 0.01: **(i)** circle plots illustrating within- and
6 between-network connections within the significant component only; **(ii)** bar plots showing the
7 sum of T-statistic strength values within the significant NBS component belonging to the
8 different intrinsic connectivity networks (i.e., seven Yeo networks and an eighth network of
9 subcortical regions), and **(iii)** within- and between-network connectivity strength (T-statistic
10 sum). Heatmaps showing total number of within- and between-network connections as a
11 percentage of the total number of connections forming the significant component: **(iv)** at p-
12 NBS-threshold = 0.01, and **(v)** p-NBS-threshold = 0.001. Statistical analyses investigating rsFC
13 differences between groups were performed using NBS, which performed mass-univariate
14 linear models (correcting for covariates age, sex, in-scanner head motion, and socio-economic
15 status) on an edgewise level.
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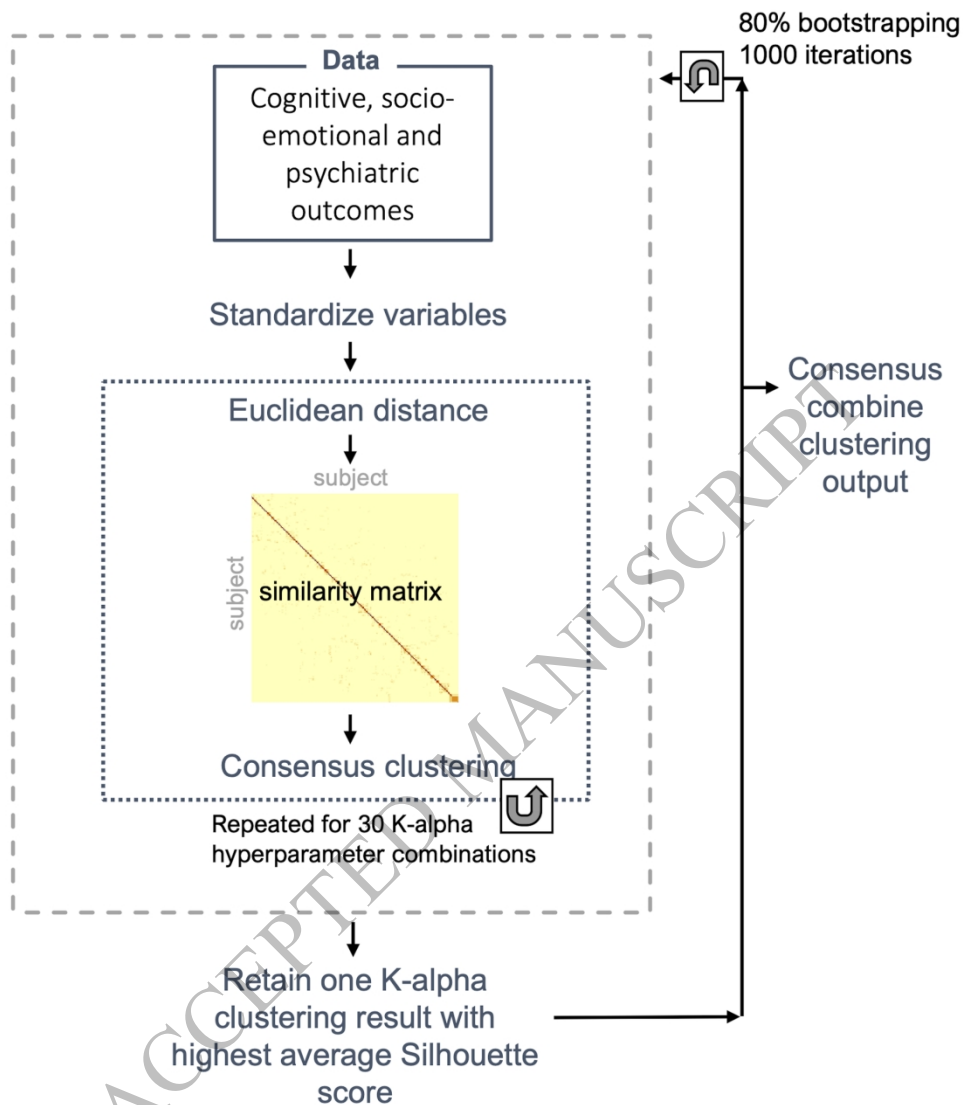


Figure 1. Consensus clustering pipeline followed.

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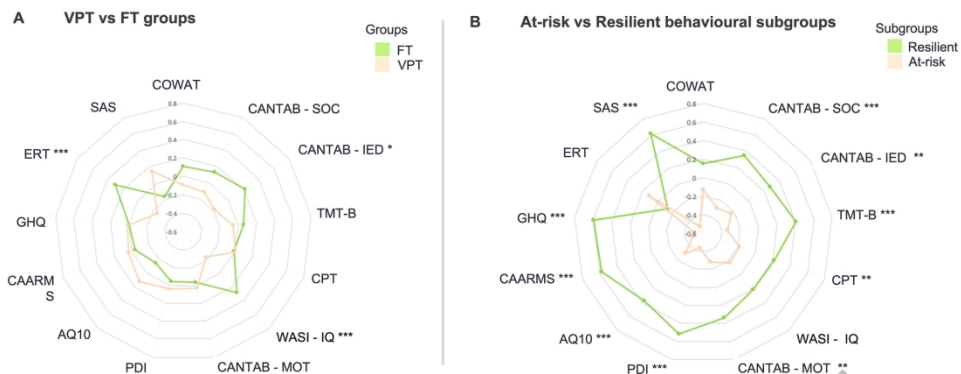


Figure 2. Radar plots showing differences in behavioural profiles between (A) VPT and FT adults and (B) At-risk and Resilient data-driven behavioural subgroups. Z-scores were computed for each group and plotted accordingly. For visual illustrative purposes, values for scales indicating poorer outcomes were reversed, so that larger Z-scores here indicate generally more optimal outcomes. *= $p < 0.05$; **= $p < 0.01$; ***= $p < 0.001$.

Statistical analyses investigating differences between groups were performed using the non-parametric Wilcoxon rank sum test. Abbreviations: AQ10 = Autism Quotient; CANTAB = Cambridge Neurophysiological Test Automated Battery; CAARMS = Comprehensive Assessment of At-Risk Mental States; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; ERT = Emotion Recognition Task; FT= full-term; GHQ = General Health Questionnaire; IED = Intra-Extra Dimensional Set Shift; MOT = Motor Screening Task; PDI = Peters Delusion Inventory; SAS = Social Adjustment Scale; SOC = Stockings of Cambridge; TMT-B = Trail Making Task B; VPT = very preterm; WASI = Wechsler Abbreviated Scale of Intelligence.

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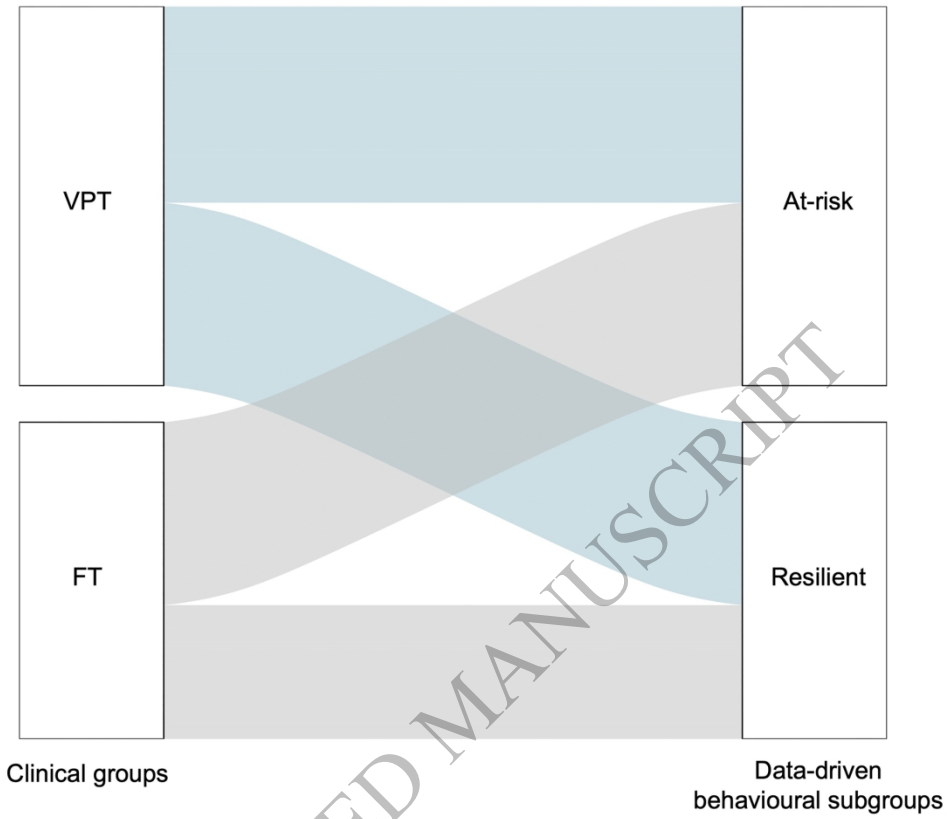


Figure 3. Alluvial plot showing VPT (in blue) and FT (in grey) adults clustering into the At-risk and Resilient data-driven behavioural subgroups.

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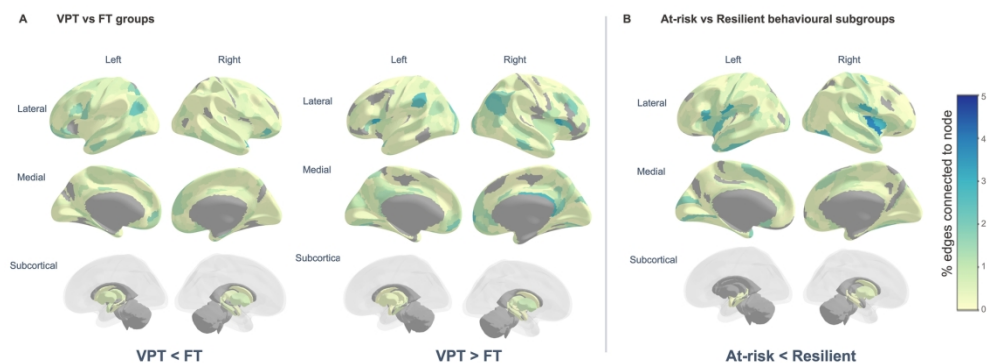


Figure 4. Percentage of edges connected to each region (i.e., node) within the significant NBS components for (A) VPT vs FT groups and (B) At-risk vs Resilient behavioural subgroups. Darker colours (blue) denote higher percentages of edges and lighter colours (yellow) denote lower percentages, with areas marked in grey indicating regions that are not forming part of the NBS component. Statistical analyses investigating rsFC differences between groups were performed using NBS, which performed mass-univariate linear models (correcting for covariates age, sex, in-scanner head motion, and socio-economic status) on an edgewise level, with the following parameters: p -NBS-Threshold = 0.01 and 1000 permutations.

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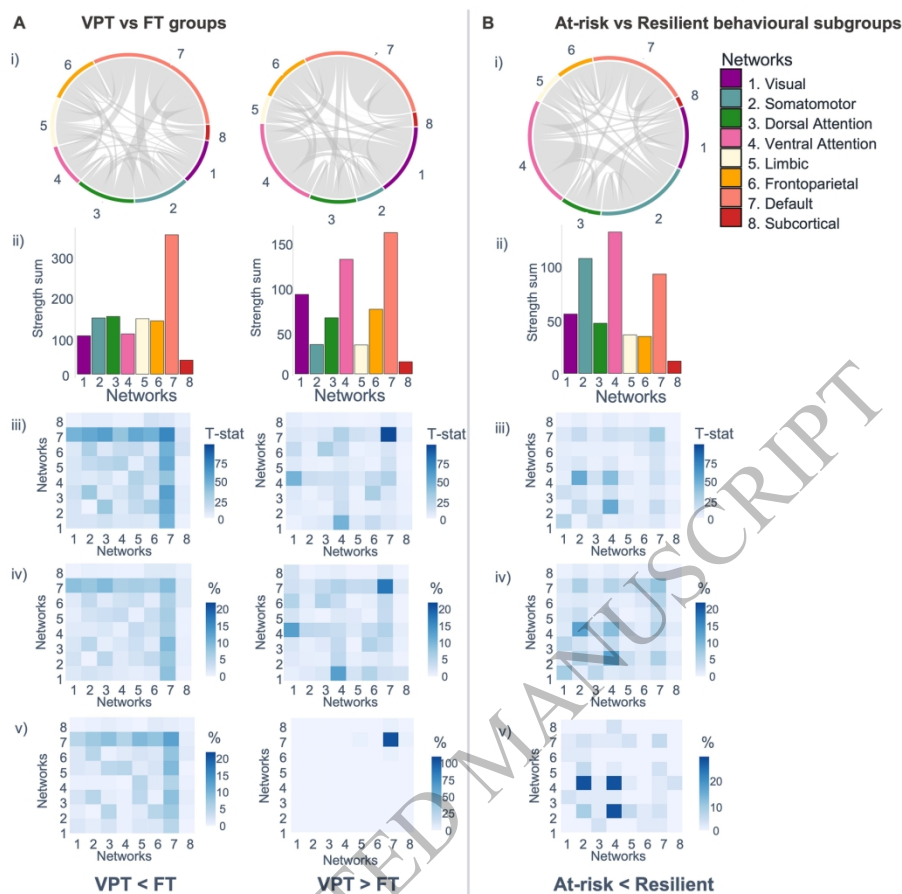


Figure 5. Within- and between-network connectivity of the significant NBS components in (A) VPT vs FT groups and (B) At-risk vs Resilient behavioural subgroups. Results from main NBS analyses using a p-NBS-threshold of 0.01: (i) circle plots illustrating within- and between-network connections within the significant component only; (ii) bar plots showing the sum of T-statistic strength values within the significant NBS component belonging to the different intrinsic connectivity networks (i.e., seven Yeo networks and an eighth network of subcortical regions), and (iii) within- and between-network connectivity strength (T-statistic sum). Heatmaps showing total number of within- and between-network connections as a percentage of the total number of connections forming the significant component: (iv) at p-NBS-threshold = 0.01, and (v) p-NBS-threshold = 0.001. Statistical analyses investigating rsFC differences between groups were performed using NBS, which performed mass-univariate linear models (correcting for covariates age, sex, in-scanner head motion, and socio-economic status) on an edgewise level.

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Table 1. Clinical and socio-demographic characteristics of study participants used for the VPT vs FT analyses

	VPT (n=116)	FT (n=83)	p-value
Gestational age at birth , median (range) weeks	30.00 (24.00 – 32.00)	n/a	n/a
Birth weight , median (range) grams	1345 (552 – 2390)	3440 (2690 – 4990)	< 0.001
Sex , n (%)			0.082
Male	66 (56.90%)	36 (43.37%)	
Female	50 (43.10%)	47 (56.63%)	
^a Ethnicity , n (%)			0.139
African	2 (1.72%)	5 (6.02%)	
Afro-Caribbean	2 (1.72%)	4 (4.82%)	
Caucasian/White	76 (65.52%)	55 (66.27%)	
Indian Subcontinent	8 (6.90%)	2 (2.41%)	
Other	4 (3.45%)	6 (7.23%)	
^b Perinatal brain injury , n (%)			n/a
No injury	62 (53.45%)	n/a	
Minor injury	27 (23.28%)	n/a	
Major injury	26 (22.41%)	n/a	
^c Parental socio-economic status , n (%)			0.220
I – II	43 (37.07%)	38 (45.78%)	
III	36 (31.04%)	15 (18.07%)	
IV – V	8 (6.90%)	3 (3.62%)	
^c Participants' socio-economic status , n (%)			< 0.001
I – II	51 (43.97%)	36 (43.37%)	
III	41 (35.35%)	26 (31.33%)	
IV – V	6 (5.17%)	0 (0.00%)	
Student	1 (0.86%)	16 (19.28%)	
Unemployed	16 (13.8%)	4 (4.82%)	
Age at assessment , median (range) years	31.37 (23.346 – 39.33)	28.73 (26.26 – 36.49)	< 0.001

^a Ethnicity was self-reported.

^b Ultrasound scans were used to classify perinatal brain injury into three categories: no haemorrhage (no injury), grade I – II periventricular haemorrhage without ventricular dilation (minor injury) and grade III – IV periventricular haemorrhage with ventricular dilation (major injury).

^c Socio-economic status was categorised according to the Office of National Statistics, 1980 occupation classifications. I: Higher managerial, administrative and professional occupations; II: Intermediate occupations, small employers and own account workers; III: Routine and manual occupations – lower supervisory and technical and semi-routine and routine occupations.

Missing data: 29 VPT and 27 FT had missing parental socio-economic status; 1 VPT and 1 FT had missing participants' socio-economic status data; 24 VPT and 11 FT had missing ethnicity data; 1 VPT has missing perinatal brain injury classification.

Table 2. Behavioural outcomes in VPT and FT adults

	VPT (n=116)	FT (n=83)	p-value	FDR p-value	Adj. FDR p-value	Effect size
^a COWAT, total words	13.00 (5.75)	14.00 (5.25)	0.052	0.166	0.115	-0.042
^a CANTAB – SOC, problems solved	9.00 (2.75)	10.00 (2.00)	0.063	0.166	0.106	-0.064
^a CANTAB – IED, total errors adjusted	15.00 (25.50)	10.50 (14.65)	0.002	0.007	0.021	0.184
^a TMT-B, time to finish task	73.50 (40.50)	71.30 (39.05)	0.081	0.175	0.068	-0.093
^a CPT, total reaction time for correct responses	417.50 (59.15)	414.00 (54.40)	0.921	0.921	0.936	-0.009
^a WASI – full scale IQ	106.00(13.75)	113.50 (12.25)	<0.001	<0.001	<0.001	0.088
^a CANTAB – MOT, reaction time	691.00 (200.80)	734.00 (196.90)	0.307	0.399	0.456	0.062
^b PDI, total score	21.50 (50.25)	18.00 (39.25)	0.406	0.480	0.530	0.002
^c AQ10, total score	2.00 (2.44)	3.00 (2.32)	0.198	0.322	0.257	0.121
^d CAARMS, general psychopathology score	2.00 (5.50)	2.00 (4.00)	0.232	0.335	0.220	-0.111
^e GHQ, total score	10.00 (6.00)	10.00 (7.00)	0.891	0.921	0.943	0.070
^a ERT, total correct	56.60 (11.15)	62.00 (9.45)	<0.001	<0.001	<0.001	0.358
^a SAS, total score	1.58 (0.45)	1.69 (0.53)	0.127	0.236	0.4021	0.136

Note. Median (interquartile range) reported. "Adj. FDR p-value" corresponds to the p-value after adjusting for covariates (sex, age, socio-economic status) and correcting for multiple comparisons with FDR. Effect sizes are calculated using Wilcoxon Glass Rank Biserial Correlation.

Missing data: ^a FT n=7, VPT n=22; ^b FT n=21, VPT n=22; ^c FT n=21, VPT n=19; ^d FT n=12, VPT n=17; ^e FT n=5, VPT n=9.

Abbreviations. AQ10 = Autism Quotient; CANTAB = Cambridge Neurophysiological Test Automated Battery; CAARMS = Comprehensive Assessment of At-Risk Mental States; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; ERT = Emotion Recognition Task; FT = full-term; GHQ = General Health Questionnaire; IED = Intra-Extra Dimensional Set Shift; MOT = Motor Screening Task; PDI = Peters Delusion Inventory; SAS = Social Adjustment Scale; SOC = Stockings of Cambridge; TMT-B = Trail Making Task B; VPT = very preterm; WASI = Wechsler Abbreviated Scale of Intelligence.

Table 3. Clinical and socio-demographic characteristics of study participants used for the clustering analyses

	VPT (n=85)	FT (n=71)	p-value
Gestational age at birth , median (range) weeks	30.00 (24.00 – 32.00)	n/a	n/a
Birth weight , median (range) grams	1317.50 (552.00 – 2390.00)		
Sex , n (%)			
Male	51 (60.00%)	33 (46.48%)	0.127
Female	34 (40.00%)	38 (53.52%)	
^a Ethnicity , n (%)			0.127
African	2 (2.35%)	5 (7.04%)	
Afro-Caribbean	1 (1.18%)	4 (5.63%)	
Caucasian/White	70 (82.35%)	53 (74.65%)	
Indian Subcontinent	7 (8.24%)	2 (2.82%)	
Other	3 (3.53%)	5 (7.04%)	
^b Perinatal brain injury , n (%)			n/a
No injury	46 (54.12%)	n/a	
Minor injury	19 (22.35%)	n/a	
Major injury	19 (22.35%)	n/a	
^c Parental socio-economic status , n (%)			0.092
I – II	39 (45.88%)	38 (53.52%)	
III	32 (37.65%)	14 (19.72%)	
IV – V	8 (9.42%)	3 (4.23%)	
^c Participants' socio-economic status , n (%)			0.006
I – II	44 (51.77%)	32 (45.07%)	
III	29 (34.12%)	23 (32.39*)	
IV – V	2 (2.35%)	0 (0.00*)	
Student	1 (1.18%)	11 (15.49%)	
Unemployed	9 (10.59%)	4 (5.63%)	
Age at assessment , median (range) years	30.90 (26.25 – 35.48)	28.85 (24.21 – 39.33)	0.002

^a Ethnicity was self-reported.

^b Ultrasound scans were used to classify perinatal brain injury into three categories: no haemorrhage (no injury), grade I – II periventricular haemorrhage without ventricular dilation (minor injury) and grade III – IV periventricular haemorrhage with ventricular dilation (major injury).

^c Socio-economic status was categorised according to the Office of National Statistics, 1980 occupation classifications. I: Higher managerial, administrative and professional occupations; II: Intermediate occupations, small employers and own account workers; III: Routine and manual occupations – lower supervisory and technical and semi-routine and routine occupations

Missing data: 6 VPT and 16 FT had missing parental socio-economic status; 1 FT had missing participants' socio-economic status data; 2 VPT and 2 FT had missing ethnicity data; 1 VPT has missing perinatal brain injury classification.

Table 4. At-risk and Resilient behavioural subgroup profiles

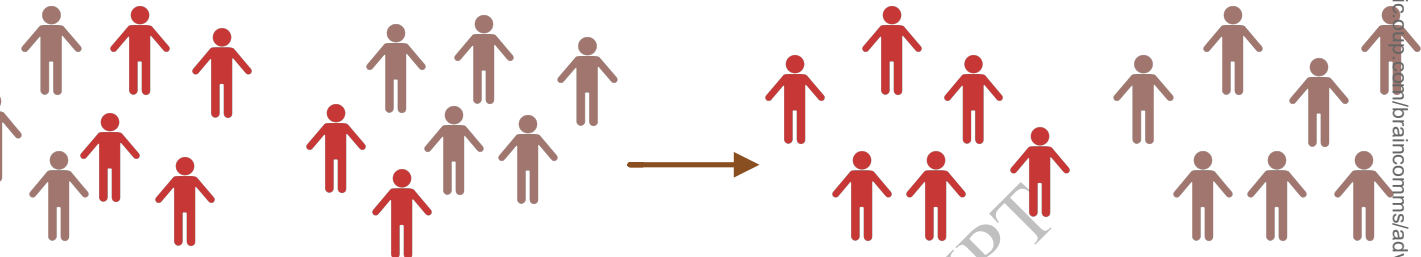
	Subgroup 1 – Resilient (n=71)	Subgroup 2 – At-risk (n=85)	p-value	FDR p- value	Adj. FDR p-value	Effect size
Age at assessment, years	29.83 (4.16)	30.22 (4.47)	0.972	0.972	n/a	-0.004
Framewise Displacement, mm	0.13 (0.07)	0.13 (0.06)	0.654	0.690	0.575	-0.042
COWAT, total words	14.00 (5.50)	13.00 (4.00)	0.071	0.097	0.117	0.168
CANTAB – SOC, problems solved	10.00 (2.00)	9.00 (2.00)	< 0.001	< 0.001	< 0.001	0.371
CANTAB – IED, total errors adjusted	10.00 (11.00)	18.00 (26.60)	0.002	0.004	0.002	-0.289
TMT-B, time to finish task	61.00 (25.20)	78.00 (39.00)	< 0.001	< 0.001	< 0.001	-0.428
CPT, total reaction time for correct responses	406.00 (51.30)	421.00 (61.40)	0.005	0.009	0.008	-0.260
WASI – full scale IQ	112.00 (15.50)	108.00 (14.00)	0.038	0.059	0.008	0.194
CANTAB – MOT, reaction time	675.00 (171.50)	741.00 (255.00)	< 0.001	< 0.001	< 0.001	-0.341
PDI, total score	13.00 (16.50)	41.80 (45.00)	< 0.001	< 0.001	< 0.001	-0.596
AQ10, total score	2.00 (1.92)	3.00 (2.71)	< 0.001	< 0.001	< 0.001	-0.385
CAARMS, general psychopathology score	0.00 (2.00)	4.60 (4.20)	< 0.001	< 0.001	< 0.001	-0.654
GHQ, total score	8.00 (2.00)	13.00 (6.00)	< 0.001	< 0.001	< 0.001	-0.663
ERT, total correct	58.40 (12.60)	60.00 (9.00)	0.112	0.142	0.132	-0.148
SAS, total score	1.44 (0.26)	1.81 (0.50)	< 0.001	< 0.001	< 0.001	-0.691
Birth status, n (%)			0.558	0.623	n/a	V = 0.060
	VPT	41 (57.75%)	44 (51.767%)			
	FT	30 (42.25%)	41 (48.24%)			
Sex, n (%)			0.169	0.200	n/a	V = 0.123
	Male	43 (60.56%)	41 (48.24%)			
	Female	28 (39.44%)	44 (51.77%)			
^a Participants' socio-economic status, n (%)			< 0.001	0.001	n/a	V = 0.365
	I – II	46 (64.79%)	30 (35.29%)			
	III	21 (29.58%)	31 (36.47%)			
	IV – V	0 (0.00%)	2 (2.35%)			
	Student	1 (1.41%)	11 (12.94%)			
	Unemployed	2 (2.82%)	11 (12.94%)			
^a Parental socio-economic status, n (%)			0.055	0.080	n/a	V = 0.208
	I – II	44 (61.97%)	33 (38.82%)			
	III	16 (22.53%)	30 (35.29%)			
	IV – V	5 (7.04%)	6 (7.06%)			

Note. Median (interquartile range) reported unless stated otherwise where number of participants (n) is reported alongside percentage (%). "Adj. FDR p-value" corresponds to the p-value after adjusting for covariates (sex, age, socio-economic status) and correcting for multiple comparisons with FDR. Effect sizes are calculated using Wilcoxon Glass Rank Biserial Correlation, unless otherwise stated. Cramer's V (V) effect size was used for categorical variables.

^a Socio-economic status was categorised according to the Office of National Statistics, 1980 occupation classifications. I: Higher managerial, administrative and professional occupations; II: Intermediate occupations, small employers and own account workers; III: Routine and manual occupations – lower supervisory and technical and semi-routine and routine occupations. Abbreviations: AQ10 = Autism Quotient; CANTAB = Cambridge Neurophysiological Test Automated Battery; CAARMS = Comprehensive Assessment of At-Risk Mental States; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; ERT = Emotion Recognition Task; FT= full-term; GHQ = General Health Questionnaire; IED = Intra-Extra Dimensional Set Shift; MOT = Motor Screening Task; PDI = Peters Delusion Inventory; SAS = Social Adjustment Scale; SOC = Stockings of Cambridge; TMT-B = Trail Making Task B; VPT = very preterm; WASI = Wechsler Abbreviated Scale of Intelligence.

Clinical groups

Stratifying heterogeneity across clinical groups



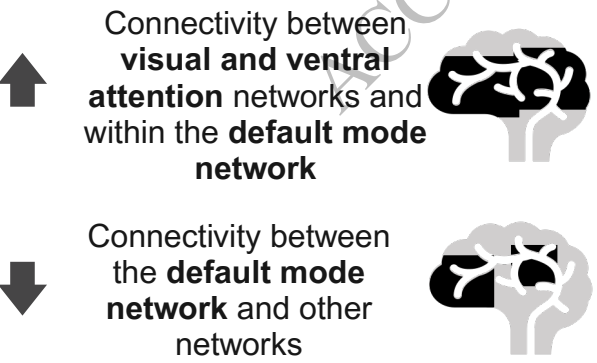
Very preterm adults

Full-term adults

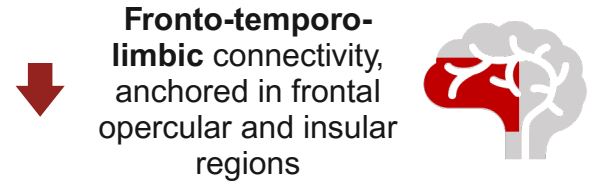
At-risk subgroup
with more behavioural difficulties

Resilient subgroup
with more favourable behavioural outcomes

Very preterm relative to full-term
functional connectivity patterns



At-risk relative to Resilient
functional connectivity patterns



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