



Altered resting-state neural networks in children and adolescents with functional neurological disorder

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ABSTRACT

Objectives: Previous studies with adults suggest that aberrant communication between neural networks underpins functional neurological disorder (FND). The current study adopts a data-driven approach to investigate the extent that functional resting-state networks are disrupted in a pediatric mixed-FND cohort.

Methods: 31 children with mixed FND and 33 age- and sex-matched healthy controls completed resting-state fMRI scans. Whole-brain independent component analysis (pFWE < 0.05) was then used to identify group differences in resting-state connectivity. Self-report measures included the Depression, Anxiety and Stress Scale (DASS-21) and Early Life Stress Questionnaire (ELSQ). Resting-state heart rate (HR) and cortisol-awakening response (CAR) were available in a subset.

Results: Children with FND showed wide-ranging connectivity changes in eight independent components corresponding to eight resting-state neural networks: language networks (IC6 and IC1), visual network, frontoparietal network, salience network, dorsal attention network, cerebellar network, and sensorimotor network. Children whose clinical presentation included functional seizures (vs children with other FND symptoms) showed greater connectivity decreases in the frontoparietal and dorsal attentional networks. Subjective distress (total DASS score), autonomic arousal (indexed by HR), and HPA dysregulation (attenuated/reversed CAR) contributed to changes in neural network connectivity. Children with FND (vs controls) reported more subjective distress (total DASS score) and more adverse childhood experiences (ACEs) across their lifespan.

Conclusions: Children with FND demonstrate changes in resting-state connectivity. Identified network alterations underpin a broad range of functions typically disrupted in children with FND. This study complements the adult literature by suggesting that FND in children and adolescents emerges in the context of their lived experience and that it reflects aberrant communication across neural networks.

1. Introduction

Functional neurological (conversion) disorder (FND) is a neuropsychiatric condition whereby children (including adolescents) present with motor, sensory, and seizure symptoms unexplained by other neurological disorders. Neuroimaging studies model FND as a multi-

network brain disorder involving alterations within and across neural networks (Perez et al., 2021). While the vast majority of research has focused on adults, FND is also common in hospital-based pediatric settings. A particular challenge when working with children (including adolescents) is the complex nature of their clinical presentations. Children commonly report antecedent adverse childhood experiences

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(ACEs) and present with multiple functional neurological symptoms (mixed FND), typically coupled with comorbid pain and comorbid nonspecific functional symptoms—fatigue, dizziness, nausea, disrupted sleep, and concentration difficulties (Ani et al., 2013; Perez et al., 2021). Comorbid mental health disorders—most commonly, anxiety or depression—vary between cohorts and are present in 22 %–80 % of patients (Vassilopoulos et al., 2022). A better understanding of the neurobiology of pediatric FND will help improve current treatment models by providing a neurobiological underpinning upon which individually tailored interventions can be based (Vassilopoulos et al., 2022). In the current study we used independent component analysis (ICA) of resting-state functional magnetic resonance imaging (rs-fMRI) to examine intrinsic functional brain networks in children with mixed FND.

In adults, the majority of rs-fMRI studies have used a seed-based approach to examine FND subgroups (functional seizures, movement disorders, persistent postural perceptual dizziness, and functional dystonia) (Perez et al., 2021). To date, only one study—with results reported across two publications—has examined resting state connectivity in adults with mixed FND ($n = 25$; 22 women) (Baek et al., 2017; Morris et al., 2017). In that study, patients (vs healthy controls) demonstrated *reduced* functional connectivity within frontal control regions (dorsolateral prefrontal cortex [dorsolateral PFC], anterior cingulate cortex [ACC], and Brodmann Area 10 in the anterior PFC) and the right inferior parietal cortex, along with *increased* functional connectivity between the premotor cortex and the supplementary motor area, and between the bilateral amygdala and right dorsolateral PFC. The limitation of the seed-based method is that it restricts connectivity analysis to specific “seed” brain regions and may not capture the complete extent of connectivity changes occurring throughout the brain in FND.

An alternate method, ICA, adopts a whole-brain exploratory approach to the analysis of imaging data by decomposing the data into independent components that correspond to neural networks and by examining connectivity between these neural networks and significant regions or clusters in the brain—referred to as component to cluster connectivity (Thomas Yeo et al., 2011). To date, the ICA studies with adult patients with FND have all been conducted with FND subgroups: functional seizures (van der Kruijs et al., 2014), functional dystonia (Canu et al., 2020), and functional hemiparesis (Monsa et al., 2018).

In 21 adults with functional seizures, Van der Kruijs and colleagues (2014) identified alterations within network connectivity, compared to controls, in four of five ICA-based networks, including the default mode network (DMN), sensorimotor network, frontoparietal network, and executive control network (van der Kruijs et al., 2014). By contrast, in a study with patients with functional dystonia ($n = 40$; 31 women; 12 patients with fixed dystonia and 28 patients with mobile dystonia), Canu and colleagues (2020) found patients with fixed functional dystonia (vs healthy controls and patients with mobile dystonia) displayed reduced connectivity within regions of the cerebellum only (Canu et al., 2020). Using an alternate clustering approach with patients with functional unilateral paresis and sensory loss ($n = 7$; 2 women), Monsa and colleagues (2018) found an increase in connectivity within the DMN only and decreased connectivity between the DMN and limbic/salience network (Monsa et al., 2018). Taken together, the above-described studies suggest that children who present with multiple FND symptoms are likely to show a wide-ranging pattern of alterations in resting-state neural networks.

Although a growing body of research studies has, over the last decade, substantially expanded our understanding of children with FND, the absence of rs-fMRI studies with these children reflects an important gap in our knowledge. Studies using electrocardiogram (ECG) and resting-state electroencephalogram (EEG) data have shown increased autonomic and cortical arousal (Kozłowska et al., 2015; Radmanesh

et al., 2020; Paredes-Echeverri et al., 2022) coupled with increased activation of nodes within the DMN (mid cingulate gyrus, posterior cingulate gyrus, and precuneus), salience network (dorsal ACC/dorso-medial PFC), and somatomotor network (left supplementary motor area) (Kozłowska et al., 2018). Task-based studies using a neurocognitive test battery suggest a shift away from cognitive processing and toward emotion processing in children with FND (Kozłowska et al., 2015; Kozłowska et al., 2013). They showed more variable reaction times, more false alarms, and more total errors on a cognitive task (the go/no-go test), and faster response times, while matching controls in accuracy, on an emotion-processing task (identification of emotion faces). A study examining cortisol awakening response (CAR)—using salivary cortisol—showed that this response was attenuated or reversed and that the degree of dysregulation correlated with the number of adverse childhood experiences (ACEs) and subjective distress (Chung et al., 2022). These findings suggest that the neural underpinnings of FND may extend across motor-sensory, arousal-processing, emotion-processing, and cognitive-processing systems.

The present study utilized ICA to investigate the full extent to which functional brain networks in children with FND may be altered in the resting state, and to examine the connectivity patterns of these networks in relation to other brain regions. Based on the above-described body of pediatric evidence, we hypothesized that in the resting state, children with mixed FND would show a brain-wide change in network organization involving one or more of the following patterns of change in neural networks:

Pattern 1: Connectivity within and between somatomotor and somatosensory networks would be weakened, thereby disrupting motor and sensory function.

Pattern 2: Connectivity between brain networks mediating cognitive control/executive functions and motor/somatosensory regions would be weakened, thereby disrupting motor, sensory, and cognitive function.

Pattern 3: Connectivity between brain networks mediating emotion-processing functions and somatomotor/somatosensory regions would be strengthened, thereby disrupting motor and sensory function.

Pattern 4: Connectivity between brain networks mediating cognitive control/executive functions and regions mediating emotion-processing functions would be strengthened, reflecting a disruption in cognitive control/executive function.

Pattern 5: Connectivity within brain networks mediating cognitive control/executive functions would be weakened, reflecting a disruption in cognitive control/executive function.

Pattern 6: Connectivity between brain networks underpinning emotion processing and regions mediating top-down control of those regions would be weakened, thereby diminishing top-down modulation of those regions.

Pattern 7: Connectivity within brain networks mediating emotion processing-functions would be strengthened, thereby enhancing arousal and stress response.

2. Methods

2.1. Participants

Thirty-two children admitted for treatment of FND to the inpatient Mind-Body Program at The Children’s Hospital at Westmead (Sydney, Australia) during the period January 2019 to July 2021 agreed to participate in the current study. All children had undergone a comprehensive neurology assessment and had been given a DSM-5 diagnosis of FND by a pediatric neurologist (American Psychiatric Association, 2013). All had participated in a biopsychosocial assessment with the mind-body team: a structured interview with the child and family

Table 1

Summary of the measures used in the study.

Measure	Description
RAHC-GAF	The Royal Alexandra Hospital for Children Global Assessment of Function (RAHC-GAF) is the DSM-IV-TR GAF modified to include functional impairment secondary to physical illness {AmericanPsychiatric, 2000 #727}. The scale has 100 points and 10 categories (10 points each). Healthy controls generally fall into the upper three brackets "superior in all areas" (score 91–100), or "good in all areas" (score 81–90). Lower values (and brackets) mark functional impairment of increasing severity. Patients with physical or psychological impairment fall into the lower brackets (score < 81).
DASS-21	The Depression Anxiety and Stress Scales (DASS-21)—total DASS score, but not the three subscales—are a validated measure of perceived distress in pediatric populations {Lovibond, 1995 #3918} {Patrick, 2010 #1636}.
ELSQ	The Early Life Stress Questionnaire (ELSQ) is a checklist of 19 stress items—and an option for elaboration—based on the Child Abuse and Trauma Scale {Cohen, 2006 #4917}. Twelve items pertain to relational stressors, including the following: bullying; physical abuse; sexual abuse; emotional abuse; neglect; parental separation; loss by separation; loss by death; family conflict; severe illness of a family member; domestic violence; and other. Other items pertain to birth complications, life-threatening/severe illness, war trauma, and natural disasters. Participants record if they have or have not experienced the given stressor and the age period during which the stressor has been experienced.

documenting the child's developmental history, history of the presenting symptoms (including comorbid nonspecific symptoms), a functional disability rating on the Global Assessment of Functioning (GAF) scale (see Table 1), and a resting-state heart rate (HR) on medical admission to the Mind-Body Program (Kozłowska et al., 2013).

On self-report the children completed the Depression Anxiety and Stress Scales (DASS-21) and Early Life Stress Questionnaire (ELSQ) (see Table 1).

Thirty-six healthy controls were recruited from the same age bracket and geographical catchment area. Control participants were screened for the absence of mental health disorders, history of head injury, family history of mental health disorders, and chronic health concerns. All controls completed the DASS-21 and ELSQ, and were rated with the GAF.

A proportion of participants (18 FND, 20 controls) participated in a parallel study examining their CAR—using salivary cortisol—a marker of hypothalamic–pituitary-adrenal (HPA) axis function (Chung et al., 2022).

The Sydney Children's Hospital Network Ethics Committee approved the study. Participants and their legal guardians provided written informed consent.

Data from four participants could not be used in the analysis. One participant with FND did not complete the resting-state component of the protocol because she had a functional seizure during the MRI procedure. Data from three control participants could not be used because of excessive motion (see section 2.3).

The clinical presentations of the final sample—31 children with FND—were diverse. They presented with one or more functional neurological symptoms (range, 1–8; mean = 3.45; median = 3.00) (Fig. 1). Length of illness ranged from 1 week to 12 months (mean = 4.24 months; median = 4.00 months): approximately-two-thirds (22/31; 71 %) having been ill for less than six months. Levels of functional disability at clinical assessment were high, with GAF scores ranging from 12 to 51 (mean = 33/100; median = 31/100) and days of school loss ranging from 0 to 20 weeks (mean = 5.44; median = 3.00) on presentation.

Two children with FND had incidental MRI findings on clinical imaging: a cyst in the subcortical white matter of the right frontal lobe and a hyperintensity in the right thalamus (both stable over time). All other clinical imaging studies (27/31; 87 %) and video EEGs (n = 21/31, 68 %, including all 13 children with functional seizures), were reported as

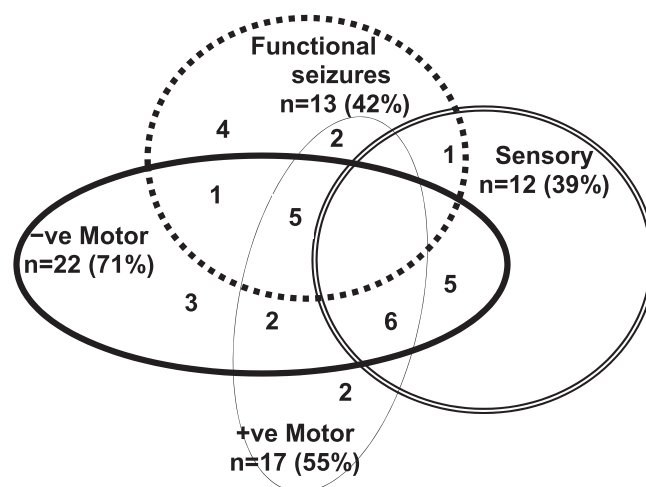


Fig. 1. Visual representation of functional neurological symptoms experienced by the children in the study cohort. Children with mixed FND commonly present with multiple functional neurological symptoms. This figure depicts the functional neurological symptoms experienced by the 31 children with FND who were included in the analysis. Negative motor symptoms included: weakness or loss of function in the limbs, aponia (loss of voice), and difficulties swallowing. Positive motor symptoms included: unusual gaits, difficulties with balance coupled with an uncoordinated gait, tics, tremors, dystonia, rumination (bringing up food via overactivation of the diaphragm), and dysphonia (change in the quality of the voice, e.g., a high-pitched baby voice). Sensory symptoms included: loss of touch, hearing, or vision. Functional seizures presented in a broad variety of ways and included faint-like events. With reference to ICA studies with adults, where patients were clustered into FND subgroups—functional seizures, functional dystonia, and functional hemiparesis—the current sample had 13 (42%) children with functional seizures, two children with dystonia (subsumed here in the positive motor symptom group), and no children with hemiparesis.

normal. Clinical characteristics are reported in Table 2.

Because of the high rate of comorbid functional, mental health, and medical conditions, many of the children (n = 25; 80.6 %) were on medication when admitted into the Mind-body Program and when the fMRI was acquired (see Table 2). Two controls were on maintenance medication for asthma, and one was on the contraceptive pill.

2.2. fMRI data acquisition

The imaging data were acquired from a 3 T Siemens PRISMA scanner (Siemens Healthcare, Erlangen, Germany) in the Radiology Department at the adjacent Westmead Hospital (Sydney, Australia), with a 64-channel head and neck array coil. Resting-state fMRI data were acquired using a simultaneous multi-slice echo-planar imaging sequence (repetition time/echo time = 1500 ms/33.0 ms, isotropic voxel size = 2.5 × 2.5 × 2.5 mm³, phase encoding direction = A-P, GRAPPA = 2, field of view = 255 mm, 60 slices of 2.5 mm thickness and whole brain coverage). During the resting-state scan, participants focused on a fixation cross for 8 min 12 sec. The structural MRI data was acquired with a 3D T1-weighted magnetization-prepared gradient echo sequence with repetition time/echo time = 2400 ms/2.21 ms; inversion time = 900 ms, field of view = 256 mm, phase encoding direction = A-P, GRAPPA = 2, flip angle = 8°, 192 sagittal slices covering the whole brain with isotropic voxel size of 0.9 mm³ and an acquisition time of 6 min 23 sec. The structural data was used for normalization of the fMRI data, as described below.

2.3. fMRI data pre-processing

Neuroimaging data were pre-processed using the CONN functional connectivity toolbox (Version 19c) and SPM 12 (<http://www.fil.ion.ucl>).

Table 2
Clinical and demographic information about participants with FND from clinical assessment.

COMORBID MEDICAL CONDITIONS		
Any comorbid medical condition	14	45 %
- Asthma/allergies	6	19.4 %
- Tourette's syndrome	2	6.5 %
- Kidney disease	2	6.5 %
- Iron deficiency	2	6.5 %
- Epilepsy (a third participant was misdiagnosed with epilepsy)	2	6.5 %
- Hypothyroid	1	3.2 %
- Recurrent tendonitis	1	3.2 %
COMORBID FUNCTIONAL SYNDROMES		
Complex (functional) pain	25	80.6 %
- Lower limbs	13	42.0 %
- Headache	10	32.3 %
- Back/neck	9	29.0 %
- Abdomen	9	29.0 %
Any comorbid functional syndrome (excluding pain)	17	54.8 %
- Functional gut disorder	13	41.9 %
- Postural orthostatic tachycardia syndrome (POTS)	7	22.6 %
- Irritable bladder	1	3.2 %
COMORBID NON-SPECIFIC SOMATIC SYMPTOMS		
Any comorbid non-specific somatic symptom	30	96.8 %
Sleep (difficulties falling asleep, waking, unrefreshing sleep)	27	87.1 %
Concentration difficulties	24	77.4 %
Dizziness	17	55.8 %
Fatigue	14	45.2 %
Nausea	14	45.2 %
Heart palpitations (thumping heart)	13	41.9 %
Breathlessness	9	29.0 %
Sweatiness	8	25.8 %
COMORBID MENTAL HEALTH DISORDERS AND SYMPTOMS		
Any mental-health disorder (DSM-5)	29	93.5 %
- Anxiety disorder	27	87.1 %
- Depressive disorder	14	45.2 %
- ADHD	4	12.9 %
- PTSD	2	6.5 %
- Learning difficulties	2	6.5 %
- Autism	2	6.5 %
MEDICATIONS AT THE TIME OF RESTING-STATE FUNCTIONAL MRI		
Any medication at the time of testing	25	80.6 %
- melatonin for sleep	16	51.6 %
- SSRI for anxiety or depression	15	48.4 %
- small doses of second-generation antipsychotics for sleep	7	22.6 %
- clonidine for sleep or to down-regulate arousal	4	12.9 %
- methylphenidate for the treatment of ADHD	3	9.7 %
- medications pertaining to a functional gut disorder (e.g., antacids, anti-constipation medications, probiotics)	8	25.8 %
- replacements for deficiencies (thyroxine, iron, vitamin D)	5	16.3 %
- antiepileptic medications for epilepsy and in one case misdiagnosed epilepsy	3	9.7 %
- gabapentin for complex/chronic pain (n = 2, 6.5 %),	2	6.5 %
- contraceptive pill	1	3.2 %
COMMON ADVERSE CHILDHOOD EXPERIENCES (ACEs) REPORTED BY THE CHILD AND FAMILY^a (maltreatment-related events are denoted by an asterisk)		
One or more ACEs (range 1–10, mean 6, SD 2.5)	31	100 %
- Bullying by peers	19	61.3 %
- Child physical illness	18	58.1 %
- Family conflict	14	49.2 %
- Maternal mental illness	13	41.9 %
- Loss via separation from a loved one or a close friend	11	35.5 %
- Loss via death of a loved one	10	32.3 %
- Maternal physical illness	7	22.6 %
- Paternal mental illness	9	29.0 %
- Paternal physical illness	5	16.1 %
- Exposure to domestic violence*	6	19.4 %
- Emotional abuse (e.g., rejection/abandonment by a parent)*	5	16.6 %
- Sexual abuse*	4	12.9 %
- Physical abuse*	1	3.2 %
- Neglect*	1	3.2 %
SOCIOECONOMIC STATUS OF THE FAMILY		
Professional	8	25.8 %
White collar	10	32.13 %
Blue collar	11	35.5 %
Unemployed	2	6.5 %
FAMILY CONSTELLATION		
Biological parents	19	61.0 %
Blended family	10	32.3 %
Lives with one parent	2	6.4 %
INTELLIGENCE QUOTA ESTIMATED FROM SCHOOL REPORTS (or formal testing)		

(continued on next page)

Table 2 (continued)

Superior range (120 +)	8	25.8 %
Average range (80–119)	18	58.1 %
Borderline range (70–79)	4	12.9 %
Delayed (<70)	1	3.2 %

*denotes maltreatment events. Over a quarter of children ($n = 9$; 29 %) reported that they had experienced some form of maltreatment (including exposure to domestic violence).

^a Bullying/social rejection by peers ($n = 19$) and illness ($n = 18$)—injury ($n = 5$); viral illness ($n = 5$); stress associated with managing a chronic medical illness ($n = 5$); severe allergic response ($n = 2$); and medical procedure ($n = 1$)—were the most common antecedent stressors, followed by parental mental illness ($n = 16$) and family conflict ($n = 14$).

ac.uk/spm). After undergoing realignment and unwarping, all fMRI images were co-registered to a standard reference image (the first volume in the dataset). Slice-timing correction was applied for temporal misalignment that may have occurred during the acquisition. The data were then normalized, segmented into tissue classes (CSF/white matter/gray matter) using the T1-weighted scan as the reference for structural data and the mean BOLD signal as the reference for functional data. The in-built CompCor method was used to extract potential noise from the cerebrospinal and white matter regions of the brain and make appropriate corrections in the functional time series. We used Artifact Detection Tools to detect motion outliers and to scrub volumes exhibiting framewise displacement above 0.9 mm. Participants were excluded from analyses if more than 25 % volumes with motion outliers (out of the 320 functional volumes) were detected (Whitfield-Gabrieli and Nieto-Castanon, 2012).

To ensure that residual motion was not a confound, mean framewise displacement values were compared between groups. There was no significant effect of motion between groups ($p = .33$).

The second-level analysis used independent component analysis, a data-driven approach that partitions the fMRI signal into individual spatiotemporal components, to investigate connectivity between the components and voxels across the whole brain.

Prior to conducting the ICA analysis, the number of components

within the dataset were estimated using the Group ICA of fMRI Toolbox (GIFT) v3.0b. The components were estimated for each participant using minimum description length criteria and then averaged to obtain the mean number of components across the entire dataset. In CONN 19c, the group-ICA analysis was run using GICA3 back-projection and G1 FastICA algorithm with a dimensionality reduction of 64 and the number of independent components set to 24 based on the value obtained from component estimation in GIFT. Subsequent to the GIFT toolbox estimating the number of ICs across the entire dataset of participants, CONN then matched up the network ICs to their corresponding neural networks in the following manner: Three Pearson's r values were assigned to each of the ICs; each r value represented the likelihood of that particular IC corresponding to a neural network; and the neural network with the strongest r value was assigned to that particular IC. This was done separately for each of the individual components. The 24 independent components were matched against a template of established large-scale neural networks in the CONN functional network atlas (Fig. 2 and Table 3). T-tests were conducted to evaluate group differences in connectivity related to each independent component. Statistical analyses were conducted using familywise error correction, voxel-wise $p < .001$ at the uncorrected level to identify significant voxels and a cluster-wise correction at $p < .05$ to determine significant clusters.

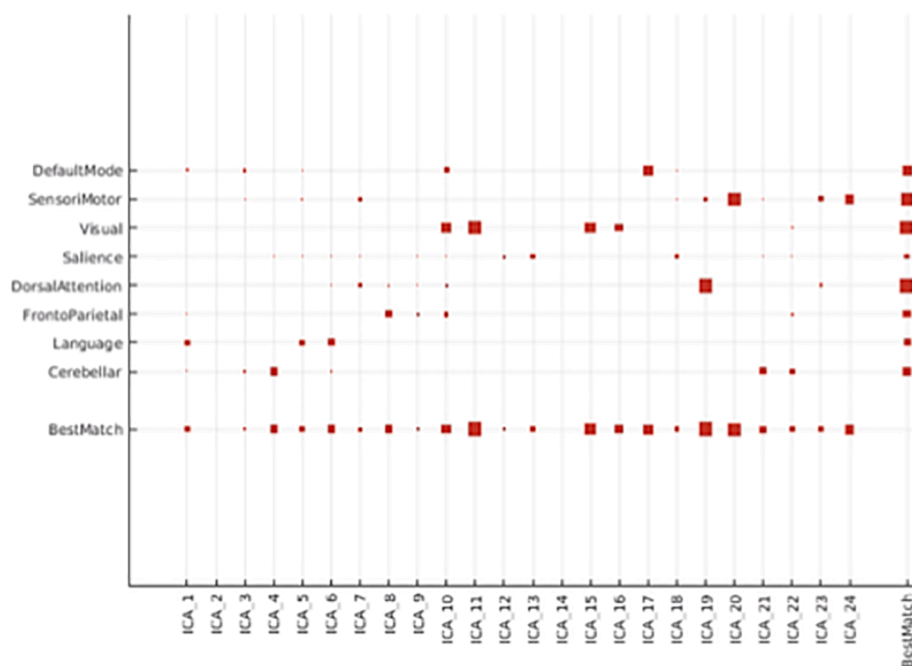


Fig. 2. The spatial matching template generated by the CONN functional atlas. This template matched up the 24 independent components across the dataset to the neural network that they best represented, using Pearson's r correlation coefficient. Bigger sized squares indicate a better match. Components 1, 6, 8, 16, 18, 19, 21 and 24 had significantly different connectivity between FND and control groups.

Table 3

Key to Independent Component Number, the Neural Network it maps onto, and the neural regions it connects with (termed component to cluster connectivity).

Components Number	Network Name	Regions Making Up the Neural Network	Neural Regions (Cluster) That the Network Connects with
Component 6	Language network	paracingulate gyrus, Inferior frontal gyrus, angular gyrus, middle temporal gyrus, inferior temporal gyrus middle frontal gyrus.	intracalcarine cortex (visual cortex) lingual gyrus (visual cortex) cuneal cortex (visual cortex) precuneus frontal pole
Component 16	Visual network	occipital pole, supracalcarine cortex, lateral occipital cortex, lingual gyrus.	
Component 1	Language network	angular gyrus, Frontal pole, middle frontal gyrus, inferior frontal gyrus inferior temporal gyrus.	middle temporal gyrus angular gyrus
Component 8	Frontoparietal network	frontal pole, middle frontal gyrus, inferior parietal lobule middle temporal gyrus.	insular cortex
Component 18	Saliience network	paracingulate gyrus, anterior cingulate gyrus, superior frontal gyrus.	Subcallosal cortex paracingulate gyrus
Component 19	Dorsal attention network	angular gyrus, precentral gyrus, precuneus, middle frontal gyrus cerebellar tonsil.	superior frontal gyrus (SFG) postcentral gyrus (somatosensory cortex) precentral gyrus (somatomotor cortex) postcentral gyrus (somatosensory cortex) precentral gyrus (somatomotor cortex)
Component 21	Cerebellar network	insular cortex, precuneus, vermis, fusiform gyrus, middle frontal gyrus cerebellum.	
Component 24	Sensorimotor network	supplementary motor area, insula, cerebellum.	postcentral gyrus (somatosensory cortex)

*The networks are shown in the order that is used in the results table.

2.4. Analysis of clinical characteristics and self-report data

Chi-square analyses and independent t-tests were used to calculate differences between the FND and control groups on categorical and continuous variables, respectively.

2.5. Post hoc analyses

Pediatric FND is a stress-related disorder whose neurology is hypothesized to involve complex interactions between lived experience, the subjective experience of that lived experience, and the biological embedding of that lived experience in the body and brain. In this context, a series of exploratory post hoc tests were run to examine a range of factors that could potentially explain or contribute to differences in neural networks.

Within the FND group we ran t-tests in relation to the following categorical variables: HR < 90 bpm vs HR ≥ 90 bpm; acute vs chronic presentation; the presence vs absence of functional seizures; clinical diagnosis of anxiety; clinical diagnosis of depression; comorbid pain; comorbid fatigue; selective serotonin reuptake inhibitor (SSRI) use; and a clinical history of maltreatment.

Also within the FND group, we used exploratory correlations to look at potential associations between altered connectivity in neural network and any of the following: autonomic arousal (using eyes-open resting-state HR; HPA function (using CAR); subjective distress (total DASS score); ACEs (total ELSQ score), duration of illness, and level of functioning (GAF).

The Shapiro–Wilk test was used to test the normality of the data. Pearson's correlations were used for normally distributed data, and Spearman's correlations were used for non-normally distributed data.

Guided by the above-described exploratory tests—and to ascertain which factors contributed to neural network modulation—we reran our

neural network comparison analyses between the FND and control groups using a general linear model (GLM) multivariate procedure with a number of factors as covariates: CAR, subjective distress (total DASS score); ACEs (total ELSQ score), duration of illness, and HR. Missing resting-state HRs for the control group were replaced with the mean HR value of 74.16 beats per minute documented in 57 healthy controls in a previous study of autonomic function in children with FND (Kozłowska et al., 2015). The control participants from the current study and the control participants from the study of autonomic function were matched on sex ($t(88) = 0.77; p = .44$) and age ($\chi^2 = 0.96; p = .33$).

To double-check that SSRI use had no effect on our findings, we also reran our neural network comparison analysis between controls and children with FND taking SSRIs and between controls and children with FND not taking SSRIs.

3. Results

3.1. Participant characteristics

The final study groups comprised 31 children and adolescents (24 girls and 7 boys) with FND aged 10.00 to 16.08 years (mean = 13.31; SD = 1.50; median = 13.42) and 33 healthy controls (27 girls and 6 boys, aged 9.25 to 17.17 years [mean = 13.96; SD = 2.1; median = 14.33]). The groups were matched for sex ($\chi^2 = 0.19; p = .66$) and age ($t(62) = -1.43; p = .16$).

Relative to controls, patients with FND had significantly higher total scores on the DASS (subjective distress) and lower scores on the GAF, and they demonstrated a more dysregulated (attenuated or reversed) CAR and HRs between the 50th and 95th centiles on an age-adjusted normative centile chart (see Table 4) (Fleming et al., 2011). On the ELSQ they reported more ACEs across their lifespans (see Table 4).

Table 4

Comparisons between FND and healthy-control groups on Global Assessment of Function (GAF), Depression Anxiety and Stress Scales (DASS-21), Early Life Stress Questionnaire (ELSQ) and cortisol awakening response (CAR).

Measure	FND group (n = 31): mean value / total score (range)	Healthy-control group (n = 33): mean value/total score (range)	t / χ^2 (p)
GAF	32.71 (12–51)	90.09 (80–99)	–32.67 (<0.001)
DASS-21 Total Score	24.42 (3–52)	5.79 0–30	6.63 (<0.001)
ELSQ	3.45 (0–9)	0.53 (0–3)	6.08 (<0.001)
CAR (nmol.min/L) (18 FND, 20 controls)	–3.78 (–267–144)	121.25 (–18–403)	–3.69 (0.001)
HR (resting state) (beats per minute)	89.45 (74–116)*	Not available	

* Resting state HR's in the FND group were shifted to the right on the normative curve (Fleming et al., 2011). The lowest resting heart rate of 74 bpm in an adolescent aged 15.67 years sits on the 50th centile and the highest heart rate of 112 bpm in a child aged 11.83 years old sits on the 95th centile. In an earlier study of autonomic function in children with FND, the mean HR in controls—comparable to the current cohort in terms of sex and age—was 74.16 bpm (range 51.01–102.03), spanning values from the 3rd centile to the 95th centile (Kozłowska et al., 2015).

3.2. Resting-state ICA differences between FND and controls

Out of the 24 independent components, group differences were observed for 8 components. Figs. 2 and 3 illustrate these independent components and the corresponding neural networks to which each of the 24 components were matched. Table 5 and Fig. 4 depict differences in

connectivity between the FND group and controls.

The FND group exhibited *increased* connectivity compared to controls in two components: Component 6 (language network) with the intracalcarine cortex, lingual gyrus, cuneal cortex, and precuneus (FWE $p < .001$); and Component 16 (visual network) with the frontal pole (FWE $p < .01$). By contrast, the FND group exhibited *decreased*

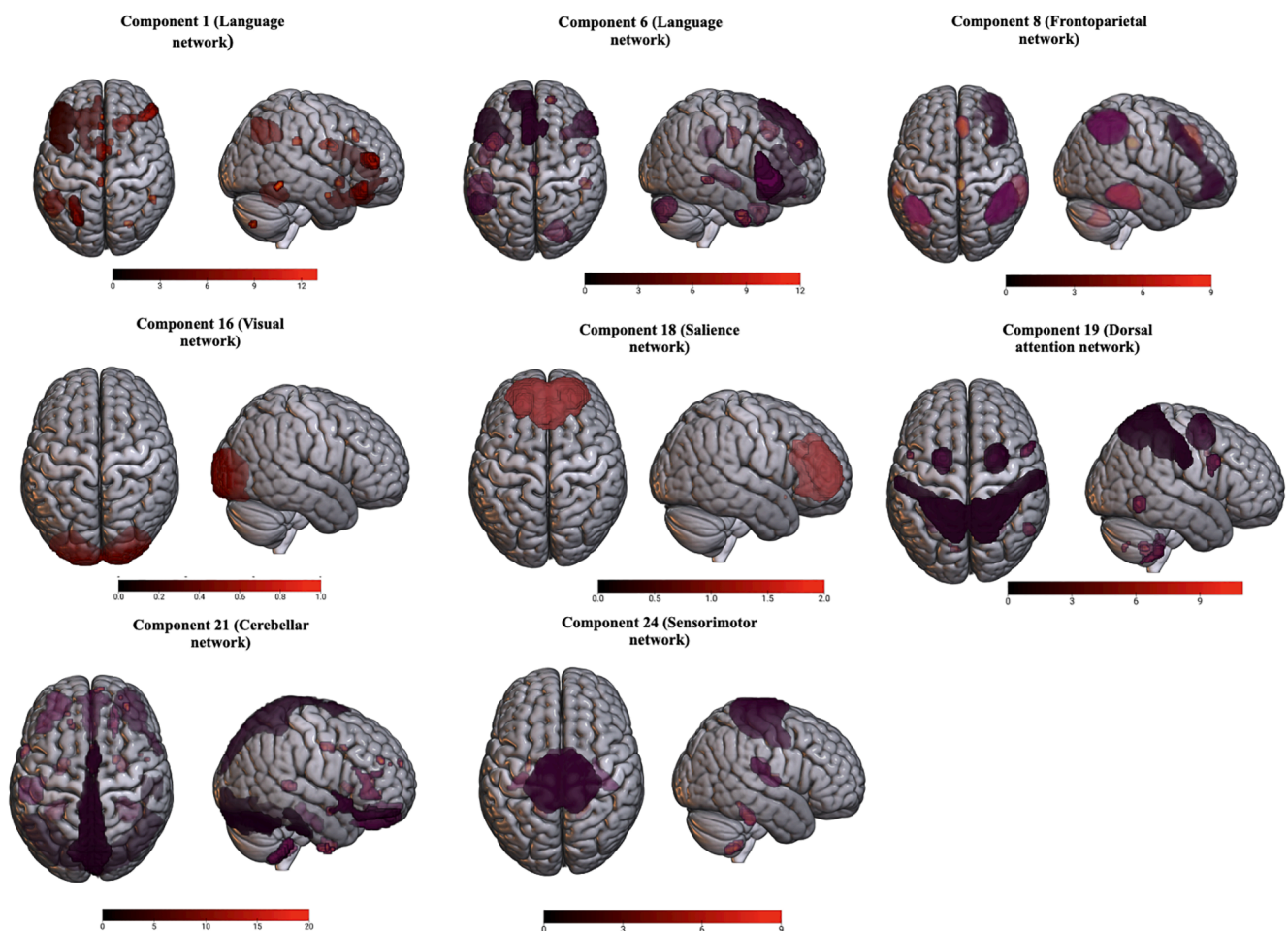


Fig. 3. Visual Representation of the significant independent components and the neural networks making up these components. For details of regions within the neural networks see Table 3.

Table 5
Group Differences in ICA Network to Cluster Connectivity between FND and Controls.

Independent component	Neural network name	MNI co-ordinates	Regions within neural network	Regions (cluster) connected to the neural network	Voxel size	T score	P value (FWE)
Connectivity FND Group > Control Group (increased connectivity)							
6	Language	04, -78, +24	Paracingulate gyrus Inferior frontal gyrus Middle temporal gyrus Inferior temporal gyrus Middle frontal gyrus	Intracalcarine cortex, Lingual gyrus, Cuneal cortex and precuneus	1901	5.26	<0.001
16	Visual	+36, +50, -04	Occipital pole Supracalcarine cortex Lateral occipital cortex Lingual gyrus	Frontal pole	144	4.89	0.01
Connectivity FND Group < Control Group (decreased connectivity)							
1	Language	+46, -52, +14	Angular gyrus Frontal pole Middle frontal gyrus Inferior frontal gyrus Inferior temporal gyrus	Middle temporal gyrus	148	6.02	0.01
8	Frontoparietal	+38, +16, +10	Frontal pole Middle frontal gyrus Inferior parietal lobule Middle temporal gyrus	Insular cortex	127	4.35	0.02
18	Saliency	+00, +22, -16	Paracingulate gyrus Anterior cingulate gyrus Superior frontal gyrus	Subcallosal cortex Paracingulate gyrus	213	4.45	<0.001
19	Dorsal attention	-20, -08, +70 + 28, -36, +50 + 28, +00, +70	Angular gyrus Precentral gyrus Precuneus Middle frontal gyrus Cerebellar tonsil	Superior frontal gyrus Postcentral gyrus Precentral gyrus	244 176 133	4.86 5.25 4.47	<0.001 <0.001 0.02
21	Cerebellar	+50, -16, +46 -48, -18, +50	Insular cortex Precuneus Vermis Fusiform gyrus Middle frontal gyrus Cerebellum	Postcentral gyrus Postcentral gyrus, Precentral gyrus	163 126	4.54 4.28	0.01 0.03
24	Sensorimotor	+40, -38, +68	Supplementary motor area Insula Cerebellum	Postcentral gyrus	143	4.75	0.02

Effects significant at corrected familywise error ($p < .05$) are shown. ICA, Independent Component Analysis; FND, Functional Neurological Disorder; MNI, Montreal Neurological Institute.

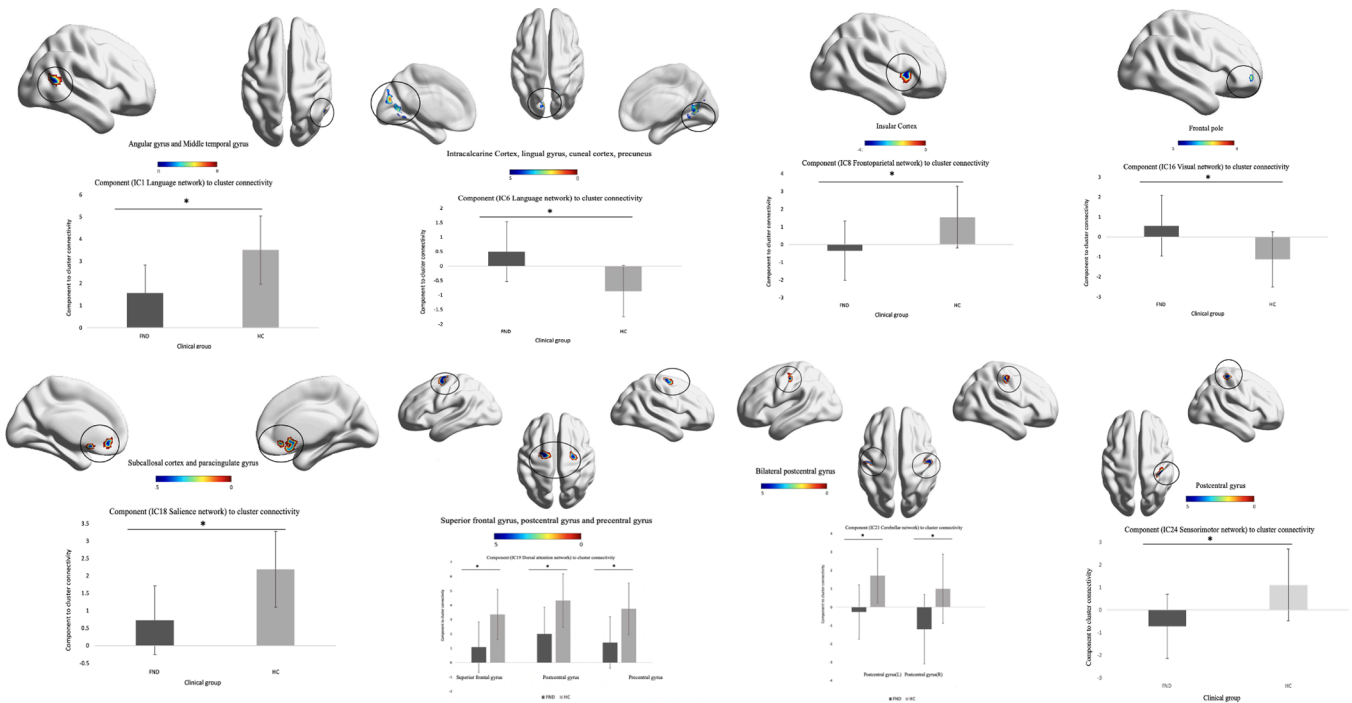


Fig. 4. Independent components with significantly different connectivity patterns between FND and controls. The FND group exhibited greater connectivity than controls in component 6 (language) and 16 (visual) networks; and lower connectivity for components 1 (language), 8 (fronto-parietal), 18 (salience), 19 (dorsal attention), 21 (Cerebellar) and 24 (sensorimotor). The term “component to cluster connectivity” refers to the connectivity between the neural network and the neural regions or cluster the network connects with (see Table 3).

connectivity relative to controls in the following 6 components: Component 1 (language network) with the middle temporal gyrus and angular gyrus (FWE $p < .01$); Component 8 (frontoparietal network) with the insular cortex (FWE $p < .02$); Component 18 (salience network) with the subcallosal cortex and paracingulate gyrus (FWE $p < .001$), 4. Component 19 (dorsal attention network) with the superior frontal gyrus (FWE $p < .001$), postcentral gyrus (FWE $p < .001$) and precentral gyrus (FWE $p < .02$); Component 21 (cerebellar network) with the postcentral gyrus (FWE $p < .01$) and the precentral gyrus (FWE $p < .03$); and Component 24 (sensorimotor network) with the postcentral gyrus (FWE $p < .02$).

3.3. Post hoc t-test analyses within the FND group

Post hoc t-test analyses within the FND group are reported in Table 6. These analyses showed the following patterns:

- Children whose FND presentation included functional seizures showed a greater decrease in connectivity between the frontoparietal network (IC 8) and insular cortex and between the dorsal attentional network (IC 19) and precentral gyrus (somatomotor cortex).
- Autonomic arousal (indexed by resting-state HR) and anxiety (clinical diagnosis of anxiety) contributed to the decreased connectivity between the cerebellar network (IC 21) and the left postcentral gyrus (somatosensory cortex).
- Pain was associated with a smaller decrease in neural network connectivity in the sensorimotor network (IC 24), suggesting that this network and its connections support the homeostatic emotions of pain.
- Fatigue was associated with a smaller decrease in neural network connectivity in the frontoparietal network (IC 8), suggesting that this network and its connections support the homeostatic emotions of pain fatigue.

There was no change in the pattern of altered connectivity in the subgroups of children with chronic presentations, clinical diagnoses of depression, or SSRI use.

3.4. Post hoc exploratory correlational analyses between clinical and neural measures within the FND group

The outcomes of the exploratory correlations and clinical measures—HR, CAR, subjective distress (total DASS score), adverse life events (total ELSQ score), duration of illness, and level of functioning (GAF score)—within the FND group are reported in Table 7 and shown visually in Fig. 5. None of these correlations was significant at a Bonferroni corrected level of 0.0008.

Notwithstanding, the analysis identified five factors that showed a p value of ≤ 0.05 and that potentially contributed to neural network connectivity. These five factors—autonomic arousal (indexed by resting-state HR), HPA axis function (indexed by CAR), subjective distress (total DASS score), adverse life events (total ELSQ score), and duration of illness—were further examined using secondary between-group analyses where each factor was run as a covariate (see section below).

3.5. Post hoc reanalysis of connectivity comparisons between the FND and controls groups while controlling for confounders

Post hoc reanalyses of connectivity differences between the FND and control groups, where factors of interest identified in the correlation analysis (see section above) were run as covariates, identified the following patterns (see Table 8):

- HPA dysregulation (CAR) contributed to modulation of neural network connectivity in 2 of the 8 networks: the visual network (IC16) to the frontal and the salience network to the subcallosal cortex and paracingulate gyrus.

Table 6
Summary of *t*-test analyses with FND subgroups.

Component Network name/ cluster	IC 6 Language	IC 16 Visual	IC 1 Language	IC 8 Frontoparietal	IC 18 Salience	IC 19 DAN\ SFG	IC 19 DAN/ Postcentral	IC 19 DAN/ Precentral	IC 21 Cerebellar/ Postcentral L	IC 21 Cerebellar/ Postcentral R	IC 24 Sensorimotor
Direction of altered connectivity in FND group as a whole	↑	↑	↓	↓	↓	↓	↓	↓	↓	↓	↓
FND subgroup <i>t</i> -test analyses	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values	t (p) mean values
Acute vs chronic presentation	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
No functional seizures vs. functional seizures	NS	NS	NS	2.25 (0.032) 0.25 vs -1.03	NS	NS	NS	2.08 (0.046) 2.07 vs 0.52	NS	NS	NS
HR < 90 bpm vs HR ≥ 90 bpm	NS	NS	NS	NS	NS	NS	NS	NS	3.57 (0.001) 0.82 vs -0.89	NS	NS
No anxiety Dx vs. anxiety Dx	NS	NS	NS	NS	NS	NS	NS	NS	2.38 (0.024) 1.27 vs -0.51	NS	NS
No depression Dx vs. depression Dx	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
No comorbid pain vs. comorbid pain	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	-2.34 (0.026) -1.91 vs -0.54
No comorbid fatigue vs comorbid fatigue	NS	NS	NS	-2.06 (0.049) -0.82 vs 0.36	NS	NS	NS	NS	NS	NS	NS
No SSRI use vs. SSRI use	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
No maltreatment vs history of maltreatment	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

DAN, dorsal attention network; Dx, diagnosis; FND, functional neurological disorder.

Acute presentations were those that were <6 months duration and chronic presentations were those that were ≥6 months duration.

Clinical diagnoses used DSM-5 criteria.

There were no differences in age or sex between FND subgroups with the exception of age and SSRI use, where children who were not medicated were slightly younger than those who were medicated with an SSRI ($t(29) = -1.29$; $p = .208$; mean 12.8 years vs 13.8 years).

Table 7
Summary of exploratory correlation analyses within the FND group.

Component Network name/cluster	IC 6 Language	IC 16 Visual	IC 1 Language	IC 8 Frontoparietal	IC 18 Saliency	IC 19 DAN/SFG	IC 19 DAN/Postcentral	IC 19 DAN/Precentral	IC 21 Cerebellar/Postcentral L	IC 21 Cerebellar/Postcentral R	IC 24 Sensorimotor
Direction of altered connectivity in FND group	↑	↑	↓	↓	↓	↓	↓	↓	↓	↓	↓
FND subgroup correlation analyses	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)	r (p)
Subjective distress (DASS-total)	NS	0.427 (0.017)	NS	NS	NS	NS	NS	-0.439 (0.013)	-0.401 (0.025)	NS	NS
HR (resting-state HR on medical admission)	NS	NS	NS	NS	NS	NS	NS	NS	-0.554 (0.001)	-0.425 (0.017)	NS
Cortisol awakening response	NS	-0.487 (0.040)	NS	NS	NS	NS	NS	NS	NS	NS	NS
Adverse Life Events (total ELSQ)*	NS	NS	NS	NS	NS	NS	NS	NS	NS	-0.361 (0.046)	NS
Duration of illness*	0.465 (0.008)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Level of function (GAF score)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

* Denotes the correlation that were non-normally distributed for which Spearman's correlation—rather than Pearson's correlation—was used. DASS, Depression Anxiety Stress Scales; ELSQ, Early Life Stress Questionnaire; FND, functional neurological disorder; GAF, Global Assessment of Functioning; HR, heart rate.

- Subjective distress (total DASS score) contributed to modulation of connectivity in 2 of the 8 neural networks: the visual network (IC 16) to the frontal pole and the cerebellar network to left and right postcentral gyri (somatosensory cortex).

Across all eight networks the number of ACEs and duration of illness did not show any direct impact on neural network connectivity (see Table 8).

And finally, an exploratory analysis of autonomic arousal (indexed by resting-state HR)—where missing HR values for controls were replaced by mean HR from a previous study of autonomic nervous system function—indicated that in 7 of the 8 neural networks, autonomic arousal contributed to modulation of connectivity (see Table 8).

3.6. Post hoc reanalysis of connectivity comparisons between FND (taking SSRIs) and controls and between FND (not taking SSRIs) and controls

SSRI use had no effect on the pattern of results. All neural network comparison analyses between controls and children with FND remained significant whether patients were mediated with SSRIs or not.

3.7. Other Spearman's correlational analyses pertaining to adverse childhood experiences

Children reporting a greater number of ACEs (total ELSQ score) reported more distress (total DASS score) ($r(29) = 0.391; p = .029$).

4. Discussion

The aim of this study was to identify changes in resting-state neural networks in children with mixed FND using a data-driven ICA approach. In line with our hypotheses, differences between the FND and control groups were found for eight neural networks with the FND group demonstrating greater functional connectivity related to the language and visual networks, and lower functional connectivity for the language, frontoparietal, saliency, dorsal attention, cerebellar, and sensorimotor networks. The subgroup of patients whose clinical presentations included functional seizures showed greater decreases in connectivity in the frontoparietal and dorsal attentional networks than children with other FND symptoms (but no functional seizures). Comorbid subjective pain and fatigue engaged the networks that included the insula: the frontoparietal network to the insular cortex and the sensorimotor network to the somatosensory cortex, respectively. Children with FND (vs healthy controls) reported a greater number of ACEs (total ELSQ score) across their lifespans and higher levels of subjective distress (total DASS score). They also showed HPA dysregulation on awakening—an attenuated or reversed CAR—and resting-state HRs lying between the 50th and 95th percentiles. Post hoc analyses suggested that subjective distress (total DASS score), dysregulation of the HPA axis (attenuated or reversed CAR), autonomic arousal (indexed by resting-state HR), ACEs, and duration of illness contributed to neural network changes. The potential implications of these findings are discussed below.

4.1. Findings relating to disrupted motor-sensory processes

Motor FND symptoms were present in 77 % ($n = 24$) of patients, and sensory FND symptoms in 38 % ($n = 12$) (see Fig. 1). In line with hypothesized pattern 1, we found a decrease in connectivity between the cerebellar network (IC 21) and both precentral gyrus (somatomotor cortex) and postcentral gyrus (somatosensory cortex), and decreased connectivity between the sensorimotor network (IC 24) and postcentral gyrus (somatosensory cortex). These findings are consistent with the broad range of motor and sensory impairments experienced by our patients.

In relation to these same findings, t-tests within the FND group showed that patients with higher HR (autonomic arousal) or clinical

diagnoses of anxiety had a greater decrease in connectivity in the cerebellar network. Along the same lines, Pearson's correlation suggested that greater subjective distress (total DASS score) was associated with lower connectivity pertaining to the cerebellar network. And secondary between-group analyses (GLM multivariate analysis) suggested that subjective distress (total DASS score) and autonomic arousal (resting-state HR) contributed to neural network modulation of both the cerebellar and sensorimotor networks (see Table 8). Taken together, these findings suggest a link between motor and emotion processing. The cerebellum—a contributor to both networks (see Table 3)—has been identified as a neural structure that lies at the intersection of emotion-motor processing, with involvement in emotion regulation, associative learning, and fear conditioning (Blakemore et al., 2016; Snow et al., 2014; Schraa-Tam et al., 2012). Blakemore and colleagues showed that in adult patients with mixed FND, the medial regions (cerebellar vermis) were engaged in patients, but not controls, during a motor task performed in an emotionally salient context (Blakemore et al., 2016). Likewise, the present study identified the cerebellar vermis as a key component of the cerebellar network. Our findings suggest that arousal levels and emotional factors may potentially contribute to the reported changes in network connectivity, reflecting emotion- and arousal-related modulation of motor-processing regions in children with FND. These findings cohere with findings from our previous EEG study with children with FND, which showed that increased autonomic arousal—a consistent finding across pediatric studies¹³—is associated with activation of neural networks (Radmanesh et al., 2020).

Another connectivity pattern (hypothesized pattern 2) was observed: decreased connectivity between the dorsal attention network (IC 19)—involved in allocating attention—and both the precentral gyrus (somatomotor cortex) and postcentral gyrus (somatosensory cortex). This finding is consistent with Yeo's observation that “sensory and motor areas are embedded within cerebral networks” (p 1150) (Thomas Yeo et al., 2011), with the consequence that changes in functional connectivity—within networks, between networks, and between networks and other brain regions—may have important flow-on effects on motor and sensory function. Interestingly, the decrease in connectivity was greater in patients whose FND presentation included functional seizures.

4.2. Findings related to disrupted cognitive processes pertaining to the language network

In line with hypothesized pattern 4, children with FND showed increased connectivity between the language network (IC6) (a brain network mediating cognitive control/executive functions) and the precuneus (a region mediating emotion-processing functions). Spearman's correlation suggested that longer duration of illness was associated with greater connectivity increases. The precuneus is involved in emotion regulation, self-agency, and self-referential processing: the spontaneous causal attributions (self-agency or lack of self-agency) that an individual makes in relation to events that elicit positive and negative emotions (Loeffler et al., 2018). Self-referential processing also affects episodic memory: the recall of memories is better when it is related to the self (Zhao et al., 2018). Of particular interest here is a recent EEG study showing the precuneus to be overactive in children with mixed FND (Kozłowska et al., 2018). Also of particular interest is that children with FND (akin to adults) show a loss of self-agency in relation to their FND symptoms—the symptoms are experienced as involuntary—and that therapeutic interventions targeting self-blaming thoughts are an important component of many treatment interventions (Fobian et al., 2020; Kozłowska et al., 2021). It is possible that increased connectivity with the precuneus reflects a disruption to cognitive control/executive functions mediated by the language network, thereby enabling the emergence of a loss of agency in relation to symptoms and an increase in negative self-attribution in relation to myriad everyday events.

Children with FND also showed a decrease in connectivity between the language network (IC1) and the middle temporal gyrus

(hypothesized pattern 5). The left and right middle and superior temporal gyri (including Wernicke's area) constitute the receptive language region (Verly et al., 2014). Decreased connectivity to these regions may suggest less efficient cognitive/integrative processing, much of which is done through thinking in symbols (words and numbers).

An unexpected finding was an increase in connectivity between the language network (IC6) and multiple regions within the visual cortex (intracalcarine cortex, lingual gyrus, and cuneal cortex). Visual regions in the occipitotemporal cortex play an important role in regulating attention, including mediation of attentional shifts. In the normal course of events, frontal regions—and especially the dorsolateral PFC—are thought to communicate with a network of higher-order association areas, to regulate attention directly by biasing processing in the occipitotemporal visual cortex, toward one dimension over another (e.g., color vs motion) (Liston et al., 2009). In the context of chronic stress, however, the functional connectivity between frontal regions and visual regions is strengthened (Liston et al., 2009). Accordingly, our findings may reflect a stress-related increase in connectivity between frontal and visual regions that bolster visual processing at the expense of cognitive-control processes that support attentional flexibility and control. This connectivity change—alongside those seen in the frontoparietal, salience, and dorsal attention networks (see below)—could presumably also contribute to the patients' difficulties in concentration (see Table 2) and in regulating their focus-of-attention. Children with FND tend to focus their attention on their symptoms, thereby amplifying them (Gray et al., 2020; Kim et al., 2022).

4.3. Findings related to disrupted cognitive processes pertaining to the visual network

Also in line with hypothesized pattern 4, children with FND showed increased connectivity between the visual network (IC 16) and the frontal pole. Pearson's correlation showed a positive association between visual network/frontal pole connectivity and subjective distress (total DASS score) and a negative association with the CAR (an attenuated or reversed CAR was associated with greater increases in the visual network). The broader literature suggests that exposure to acute stress is generally associated with an increase in CAR, and that chronic, prolonged, uncontrollable, or traumatic stress is associated with an attenuation in CAR (Filaire et al., 2013). Finally, children reporting a greater number of ACEs (total ELSQ score) also reported more distress (total DASS score).

Secondary between-group analyses (FND vs controls) using the GLM multivariate analysis likewise suggested that subjective distress (total DASS score), autonomic arousal (indexed by resting-state HR), and HPA axis dysregulation (attenuated or reversed CAR) all contributed to the increased connectivity of the visual network. Between-group findings were no longer significant when controlling for these factors (when the factors were run as covariates) (see Table 8).

The visual network is an information-processing network that is available early in development—from birth onward (Simion and Giorgio, 2015). It is implicated in processing visual information pertaining to external stimuli (e.g., facial emotional expressions) and—later on, with development—with visual information pertaining to internally generated mental images. Orr and colleagues (2015) were the first to document the important structural (white matter) connection between the posterior visual cortex and frontal pole (Orr et al., 2015). They proposed that the ventral frontal pole is well positioned to guide attention and behavior related to linking stimuli to values and emotions (prioritizing emotion processing), whereas the lateral dorsal regions of the frontal pole, which connect up with lateral prefrontal regions, was well positioned to guide attention and behavior related to the overall goals and plans (prioritizing cognitive processing) (pp 20, 23) (Orr et al., 2015). The modulation of this network by subjective distress, autonomic arousal, and HPA dysregulation suggests that children with FND present with a stress-induced activation/dysregulation of the stress system and

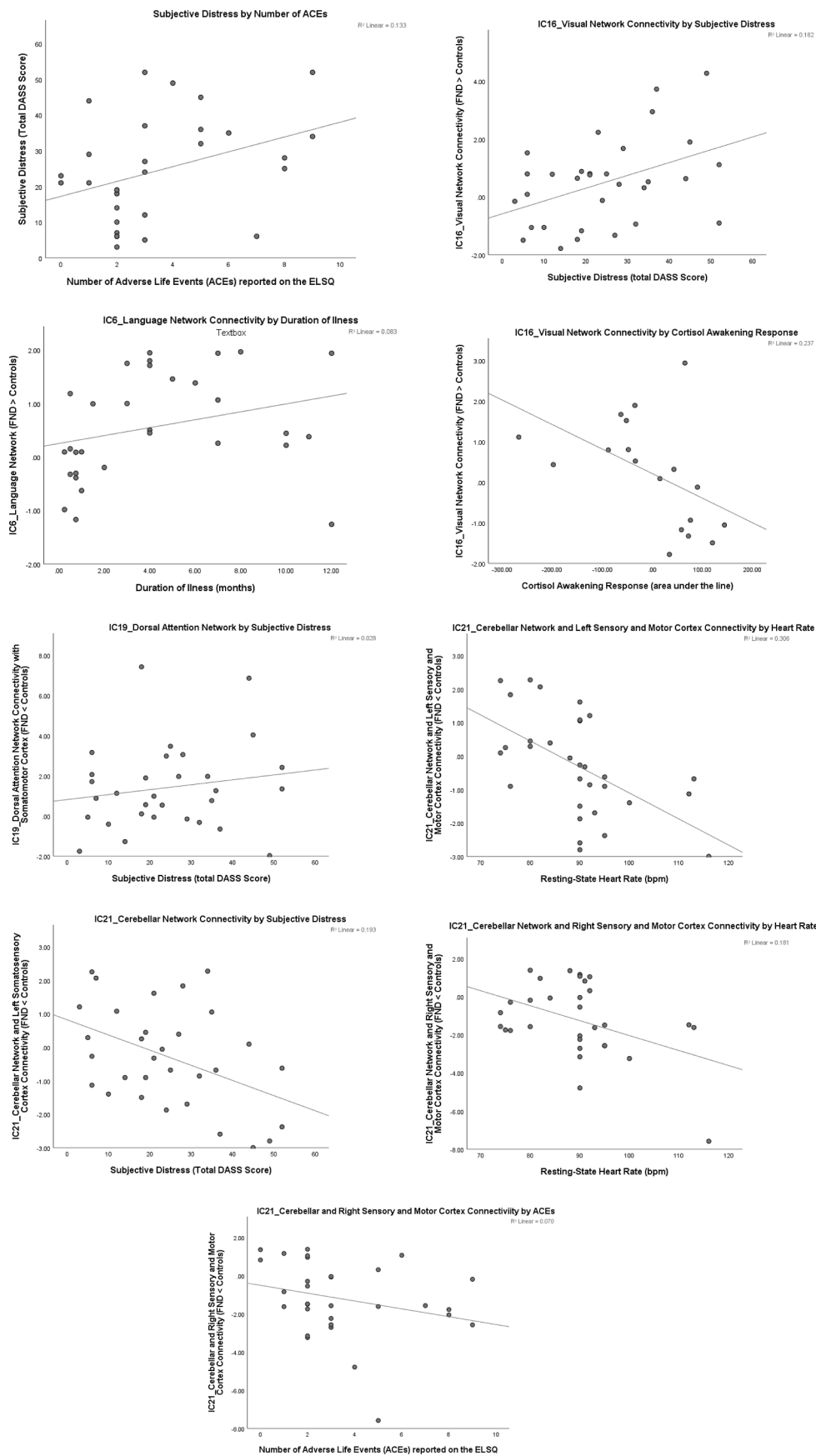


Fig. 5. Scatter Plot Visual Representations of Correlation Analyses.

Table 8

Group Differences in ICA Network Connectivity between FND and Controls with CAR, DASS, ACEs, and illness duration, and HR as covariates.

Independent component	Neural network name	MNI co-ordinates	Voxel size	T score	P value (FWE)	P value with CAR as covariate	P value with ACEs as covariate	P value with DASS score as covariate	P value with Illness duration as covariate	P value with HR* as covariate
6	Language	04, -78, +24	1901	5.26	<0.001	<0.001	<0.001	<0.001	<0.001	0.055
16	Visual	+36, +50, -04	144	4.89	0.01	0.132	0.003	0.109	0.003	0.119
1	Language	+46, -52, +14	148	6.02	0.01	0.030	<0.001	0.001	<0.001	0.465
8	Frontoparietal	+38, +16, +10	127	4.35	0.02	0.035	0.004	0.015	0.004	0.823
18	Saliency	+00, +22, -16	213	4.45	<0.001	0.013	0.001	<0.001	0.001	0.104
19	Dorsal attention	-20, -08, +70 + 28, -36, +50 +	244 176	4.86 5.25	<0.001 <0.001	0.003 0.001	<0.001 0.004	<0.001 0.002	<0.001 0.004	0.212 0.910
21	Cerebellar	28, +00, +70 +50, -16, +46 -48, -18, +50	133 163 126	4.47 4.54 4.28	0.02 0.01 0.03	0.001 0.002 0.012	<0.001 <0.001 0.013	<0.001 0.097 0.105	<0.001 <0.001 0.003	0.689 0.006 0.016
24	Sensorimotor	+40, -38, +68	143	4.75	0.02	0.011	0.001	0.001	0.001	0.930

*The HR analysis is was run with resting-state HR's from the FND group and a mean HR values of 74.6 bpm for controls derived from controls from a previous autonomic system study. It was an exploratory analysis run to examine the potential role of arousal in modulating the neural networks.

Effects significant at corrected familywise error ($p < .05$) are shown.

CAR, Cortisol Awakening Response; DASS, Depression Anxiety Stress Scales; FWE, familywise error; ICA, Independent Component Analysis; FND, Functional Neurological Disorder; HR, heart rate; MNI, Montreal Neurological Institute.

that they prioritize emotion processing to guide attention and behavior. This interpretation is consistent with the findings of faster reaction times (with good accuracy) during an emotion-processing task and more varied times (with more mistakes) during a cognitive task (Kozłowska et al., 2015; Kozłowska et al., 2013).

Of particular interest here is a recent study looking at the relationship between gene expression and brain organization/reorganization in adult patients with FND (Diez et al., 2021). The study showed that increased functional connectivity within the visual cortex was influenced by ACEs (in this case physical abuse) (Diez et al., 2021). In the present study subjective distress (total DASS score) was positively correlated with increased connectivity in the visual cortex and children reporting more distress (total DASS score) also reported a greater number of ACEs (total ELSQ score).

Considered together, these data hint at complex biological processes involving the stress system (including the autonomic system and HPA axis) that may allow adverse life experiences to be biologically embedded and come to be expressed in altered neural network connectivity patterns. Potential pathways have been discussed elsewhere (Chung et al., 2022; Diez et al., 2021; Agorastos et al., 2019; McEwen et al., 2015).

4.4. Findings related to disrupted cognitive processes pertaining to the dorsal attention network

Children with FND showed a decrease in connectivity between the dorsal attention network (IC 19) and the superior frontal gyrus (hypothesized pattern 5). The dorsal attention network is involved in allocating attention. The superior frontal gyrus is involved in cognitive control/executive functions, including working memory (Niendam et al., 2012). Decreased connectivity within this system is consistent with compromised cognitive control/executive functions supported by the dorsal attention network and may potentially contribute to the difficulties with focus of attention and concentration experienced by our patients (see discussion above and Table 2).

Secondary analyses suggested that subjective distress (Pearson's correlation) and autonomic arousal (GLM multivariate analysis) potentially contributed to the decreased connectivity of the dorsal attention network (see Tables 7 and 8).

4.5. Findings related to disrupted cognitive processes pertaining disrupted top-down modulation (inhibitory) functions

Top-down modulation processes play an important role in regulating

arousal, feelings states (pain, fatigue, and feelings proper), and thoughts processes. Potential disruption of top-down modulation—hypothesized pattern 6—was evidenced by decreased connectivity between the frontoparietal network (IC 8), a network involved in top-down control functions and attentional control functions (Liston et al., 2009) and the insular cortex. Secondary analyses (GLM multivariate analysis) suggested that subjective distress (total DASS score) and autonomic arousal (indexed by resting-state HR) potentially contributed to the decreased connectivity of the frontoparietal network (see Table 8).

The insular cortex is involved in salience detection and in representing internal bodily awareness (homeostatic feelings, the felt sense of the body, including fatigue, effort, and pain) (Craig, 2013). These homeostatic feelings (termed *somatic markers*), in turn, influence decision making and error prediction (Craig, 2013; Damasio, 1996; Bechara and Damasio, 2005; Kleckner et al., 2017). Although we cannot claim causality from our analysis of resting-state data, this reduced connectivity pattern could reflect a weakening of top-down modulation of the insula, thereby contributing to the children's difficulties in modulating the homeostatic emotions of pain (80.6 % of this sample) and fatigue (42.2 % of this sample). Of interest is that the decrease in connectivity was more marked in patients with functional seizures, which are often triggered by pain and which occur with greater frequency in the context of fatigue (i.e., later in the day, when the child is fatigued).

Potential disruption of top-down modulation—hypothesized pattern 6—was also evidenced by a decrease in connectivity between the salience network (IC 18) and the subcallosal cortex and paracingulate gyrus. The subcallosal cortex, part of the medial PFC, is involved in top-down inhibition of amygdala responsiveness to fearful cues (Vermetten and Lanius, 2012). Decreased connectivity within this system is likely to contribute to the high levels of arousal observed in children with FND (Kozłowska et al., 2015; Radmanesh et al., 2020; Kozłowska et al., 2017). The secondary GLM multivariate analysis suggested that autonomic arousal (indexed by resting-state HR) contributed to the decreased connectivity of the salience network (see Table 8).

The paracingulate gyrus, also part of the medial PFC, is involved in cognitive control functions, including successful interference resolution, the ability to suppress goal-irrelevant inputs—including inhibition of inappropriate thoughts and memories—while selecting and organizing goal-relevant inputs (Zhang et al., 2017; Deng et al., 2018). Hence, the decreased connectivity pattern may contribute to the difficulties that children with FND have in managing illness-promoting cognitions (self-blaming thoughts, catastrophizing, and rumination) (Fobian et al., 2020; Kozłowska et al., 2021).

4.6. Hypothesis related to increased connectivity within brain networks mediating emotion processing

Our data-driven analysis did not show any findings pertaining to hypothesized pattern 7.

5. Limitations

Our study has several limitations. The most important limitation is the lack of concurrent ECG data during the MRI procedure, which could have provided in-the-moment information pertaining to arousal (measures of HR and heart rate variability) for all participants in the current cohort. In the above-reported analysis, we used resting-state HR documented on admission (FND group) and mean resting-state HR documented in 57 control participants from a previous study (control group). Concurrent acquisition of autonomic measures will be an important addition to future studies. A second limitation is the lack of concurrent EEG data. In a previous study we showed that in children with FND, increases in autonomic arousal are reflected in neural network activation. It would have been helpful to examine whether this coupling was also present in the current study. A third limitation (difficulty) is the complexity of disentangling the complex, nonlinear biological pathways that are hypothesized to underpin FND and other stress-related disorders (Chung et al., 2022; Diez et al., 2021; Agorastos et al., 2019; McEwen et al., 2015). It is challenging to elucidate the contribution of multiple interacting factors—stage of development, biological embedding of experience, comorbidities, medication effects, and so on—and the biological pathways by which all these factors contribute to the picture. In the current study we used a range of post hoc analyses—within group t-tests, correlation analyses, and GLM multivariate analyses—in our attempt to examine this complex picture. A fourth limitation is the lack of a follow-up fMRI to investigate whether neural networks normalized or partially normalized following treatment. A longitudinal fMRI model could be a potential research avenue. A fifth limitation is the lack of functional data—task-based fMRI and cognitive-behavioral data—which, if available for this cohort, would enable us to better understand the functional implications the resting-state network findings presented in the current study. A sixth limitation is that the children who participated in this study were not medication free (see Table 2). Medication heterogeneity and sample size did not allow for sub-analysis to examine medication effects (with the exception of the SSRI's). A final limitation is that—with the exception of children with functional seizures—our cohort was not large enough to include other homogeneous FND presentations that could have been examined as meaningful subgroups.

6. Conclusions

Children presenting with FND show wide-ranging changes in resting-state neural network connectivity. The identified network changes are known to underpin a broad range of functions that are typically disrupted in children with FND: motor and sensory functions, self-agency processes, salience detection and the felt sense of the body, regulation of attention, regulation of arousal, regulation of feelings states, and cognitive control/executive functions. Our findings suggest that subjective distress (total DASS score), autonomic arousal (indexed by elevated resting-state HR), and dysregulation of the HPA axis (attenuated or reversed cortisol awakening response) contribute to altered connectivity across multiple neural networks. A reasonable inference is that through complex biological processes, the child's lived experience is biologically embedded and comes to be expressed in altered neural network connectivity patterns. This pediatric study adds to a growing literature that models FND as a multi-network brain disorder involving alterations within and across neural networks (Perez et al., 2021).

7. Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Author contributions

SF, KG,IB, KK, and MK contributed to study conceptualization and methodology; SF and KK contributed to recruitment, project administration, data acquisition and curation; SR, KK, and MK contributed to formal data analysis; KK wrote the original draft; and all authors contributed to the review, criticism, and rewriting of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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