Title: Fronto-parietal effective connectivity during working memory in Neurofibromatosis Type 1 adolescents and neurotypical controls.

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Data/code availability: The patient data have been deposited on the Sage Bionetworks data repository https://www.synapse.org/. Approved researchers can request to obtain the data which are subject to data sharing agreements. Codes for data processing and analysis are available at https://github.com/MCLit/NF1-DCM-WM.

Ethics statement: Ethics approval for the study was obtained from the North West-Greater Manchester South Research Ethics Committee (reference: 18/NW/0762). Written informed consent was obtained from the parents and older adolescent participants and assent was obtained from the younger participants.

Conflict of Interests: None of the authors have a conflict of interest to disclose

Key words: Neurofibromatosis, working memory, effective connectivity, functional MRI.

Abstract

Background

Neurofibromatosis Type 1 (NF1) is a rare, a single-gene neurodevelopmental disorder. Atypical brain activation patterns have been linked to working memory difficulties in NF1 patients. The present work investigated if greater inhibitory activity underlies in interactions between neuronal populations in NF1 patients, as estimated with effective connectivity during working memory ask.

Methods

Forty-three adolescent patients with NF1 and twenty-six age-matched neurotypical controls completed functional magnetic resonance imaging scans during a verbal working memory task. Dynamic causal models were estimated for bilateral fronto-parietal network (dorsolateral and ventrolateral prefrontal cortices (dlPFC and vlPFC), superior and inferior parietal gyri (SPG and IPG)). Parametric empirical Bayes approach with Bayesian model reduction was used to test the hypothesis that NF1 diagnosis would be characterised by

greater inhibitory self-connections (intrinsic connectivity). Leave-one-out cross-validation (LOO-CV) was performed to test the generalisability of group differences.

Results

NF1 participants have greater average connectivity of left dlPFC, IPG, SPG and bilateral vlPFC. The winning model of Bayesian model reduction investigating effects of working memory showed that NF1 patients have stronger intrinsic connectivity of left vlPFC, but weaker connectivity of right vlPFC and left dlPFC. The parameters of these connections were weakly predictive of NF1 diagnosis; correlation coefficient between true and predicted scores was 0.19 ($p = 0.055$)

Conclusions

Increased average connectivity of left dlPFC, IPG, SPG and bilateral vlPFC in NF1, suggests greater overall sensitivity of these regions to inputs. Working memory evoked different patterns of input processing in NF1, that cannot be characterised by increased inhibition alone. Instead, modulatory connectivity related to working memory showed more inhibitory self-connectivity of left dlPFC and left vlPFC, and less inhibitory intrinsic connectivity of right vlPFC in NF1. Importantly, this discrepancy between average and modulatory connectivity suggests that overall NF1 participants are responsive to cognitive task-related inputs but may show atypical adaptation to the task demands of working memory.

Introduction

Neurofibromatosis Type 1 (NF1) is a single-gene autosomal dominant neurodevelopmental disorder with birth incidence of 1:2,700 Evans et al. (2010). Patients with NF1 may develop pigmentary lesions, dermal neurofibromas, skeletal abnormalities, brain and peripheral nerve tumours, learning disabilities, and cognitive and social deficits (Gutmann et al., 2017). The condition is caused by mutations to the NF1 gene, which regulates the RasMAPK molecular pathway and encodes the neurofibromin protein (Daston & Ratner, 2005; North et al., 1997). Within the central nervous system, neurofibromin contributes to levels of GABA-ergic activity (Costa et al., 2002). Mouse models of NF1 suggest elevated inhibition during task performance (Shilyansky et al., 2010), where increased GABA-ergic activity disrupts neurological development during the critical periods (van Lier et al., 2020). Further, in humans NF1 is associated with morphological atypicality, such as increased grey and white matter volumes and white matter hyperintensities (Buratti et al., 2012; Payne et al., 2010; Petroff, 2016).

NF1 has been associated with a variety of cognitive, behavioural, and social disruptions. NF1 patients tend to perform more poorly in academic settings than their siblings without NF1 diagnosis (Lehtonen et al., 2012). This includes poorer performance on assessments of intelligence, visuospatial skills, social competence, executive function and attention. Notably, the NF1 condition has been characterised by working memory disruptions. Working memory refers to the ability to store and manipulate information over a short period of time (Baddeley, 1992; Baddeley et al., 2014). It is essential for adaptive behaviour and it has been related to academic performance, including performance in mathematics, literacy, and language comprehension (Gathercole & Alloway, 2005).

Shilyansky et al. (2010) demonstrated that NF1 patients are less accurate on working memory tasks than controls, and they show more pronounced slowing effect of increased memory load on response times than controls. Shilyansky et al. (2010) explored the neural substrates of these patterns with functional Magnetic Resonance Imaging (fMRI) and demonstrated that deficits in working memory of NF1 patients were associated with hypoactivity in dorsolateral prefrontal cortex (dlPFC), frontal eye fields, and parietal cortex, and striatum. Similarly, Ibrahim et al. (2017) have demonstrated that atypical patterns of fronto-parietal functional connectivity during working memory task was predictive of behavioural outcomes.

This work aims to explore how neuronal populations in the fronto-parietal network interact with each in other in NF1 as compared to controls. These aims will be fulfilled with dynamic causal modelling (DCM) of fMRI data obtained during verbal working memory task (N-back task) from adolescent patients with NF1 diagnosis and age-matched neurotypical controls. DCM is a method of inferring directed interactions between neuronal populations (effective connectivity) and characterising them as excitatory or inhibitory (Zeidman, Jafarian, Corbin, et al., 2019). Further, DCM can be used to estimate the intrinsic connectivity of a region, which reflects the self-inhibition in the region or equivalently its sensitivity to inputs (Snyder et al., 2021). Importantly, the intrinsic connectivity can be interpreted as controlling the excitatory-inhibitory (E/I) balance in the given region. The E/I balance is maintained by GABA-ergic activity (Maffei et al., 2017), and it is hypothesised that the increased levels of GABA underlie compromised E/I balance in NF1 patients (Buratti et al., 2012; Payne et al., 2010; Petroff, 2016). Therefore, we hypothesize that patients will have more inhibitory intrinsic connectivity during working memory than controls.

Methods

NF1 Participants

Part of the data used here is from a previous study described in detail in Garg et al. (2022). Forty-three adolescents aged 11–17 years were recruited via the Northern UK NF-National Institute of Health, with (i) diagnostic criteria [National Institutes of Health Consensus Development Conference. Neurofibromatosis conference statement. Arch. Neurol. 45, 575–578 (1988).] and/or molecular diagnosis of NF1; (ii) no history of intracranial pathology other than asymptomatic optic pathway or other asymptomatic and untreated NF1-associated white matter lesion or glioma; (iii) no history of epilepsy or any major mental illness; and (iv) no MRI contraindications. Participants on pre-existing medications such as stimulants, melatonin or selective serotonin re-uptake inhibitors were not excluded from participation. The study was conducted in accordance with local ethics committee approval (Ethics reference: 18/NW/0762, ClinicalTrials.gov Identifier: NCT0499142. Registered 5th August 2021; retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04991428). All methods were carried out in accordance with relevant guidelines and regulations.

Neurotypical controls

Twenty-six adolescents with no diagnosis of NF1 were recruited. Controls' age and sex were matched to the sample of NF1 patients. Table 1 includes demographics information for NF1 patients and controls.

Table 1 Demographic data of study participants (43 NF1 patients, 26 controls).

	Mean Age (STD)	Sex (M/F)
NF1 Patients	14.8 (1.83)	22/21
Controls	14.15 (2.71)	12/14

Experimental Procedure

Participants laid in the scanner and a T1-weighted image was acquired. Participants were asked to perform a working memory task for 6 min while fMRI scans were acquired. In addition, T2-weighted images were acquired at the first visit (after the T1 image) and reviewed by a paediatric neuro-radiologist to rule out NF1 associated tumours.

The working memory task session consisted of 6 blocks each of 0-back and 2-back verbal working memory task. During the 0-back condition, participants were instructed to press a hand-held button only when the letter 'X' was presented on the screen. For the 2-back condition, the participants were instructed to press the same button when the letter on the screen matched the letter 2 presentations before. Each block was 30 seconds long and consisted of 9 target stimuli.

Image acquisition

Imaging was performed on a 3 Tesla Philips Achieva scanner using a 32-channel head coil with a SENSE factor 2.5. To maximise signal-to-noise (SNR), we utilised a dual-echo fMRI protocol developed by Halai et al. []. The fMRI sequence included 36 slices, 64×64 matrix, field of view (FOV) 224×126×224 mm, in-plane resolution 2.5×2.5 mm, slice thickness 3.5 mm, TR=2.5 s, TE = 12 ms and 35 ms. The total number of volumes collected for each fMRI run was 144.

Image Processing

Image processing was done using SPM12 (Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) and MATLAB R2023a. Dual echo images were extracted and averaged using in-house MATLAB code developed by Halai et al. (2014) (DEToolbox). First, functional images were slice time corrected and realigned to first image. Then, the short and long echo times were combined for each timepoint. The orientation and location of origin point of every anatomical T1 image was checked and corrected where needed. Mean functional EPI image was co-registered to the structural (T1) image. Motion parameters estimated during co-registration of short images were used as input to the Artifact Detection Tools (ART; https://www.nitrc.org/projects/artifact_detect/) toolbox along with combined dual echo scans for identification of outlier and motion corrupted images across the complete scan. The outlier detection threshold was set to changes in global signal 3 standard deviations away from mean global brain activation. Motion threshold for identifying scans to be censored was set to 3 mm. Outlier images and images corrupted by motion were censored during the analysis by using the outlier volume regressors. Subjects with <80% of scans were removed from analysis. Following removal of participant data with high motion and artefacts, 16 controls and 28 NF1 patients remained. Unified segmentation was conducted to identify grey matter, white matter, and cerebrospinal fluid. Normalisation to MNI space was done with diffeomorphic anatomical

registration using exponentiated lie-algebra (DARTEL) (Ashburner, 2007) registration method for fMRI. Normalised images were interpolated to isotropic 2.5 × 2.5 × 2.5 mm voxel resolution. A 6x6x6mm full width at half maximum (FWHM) Gaussian smoothing kernel was applied.

fMRI analysis

For each subject, a canonical hemodynamic response function was fitted for 0-back and 2-back conditions of N-back task and general linear model (GLM) was estimated. A high-pass filter with a cut-off at 128 seconds was applied to remove slow signal drifts. An autoregressive model (AR(1)) was fitted to estimate and remove serial correlations. Global masking threshold remained at default 0.8 value. The volume censoring regressors and 6 motion parameters were included as covariates in the model. One F-contrast of main effect of condition was defined, followed by a 2-back>0-back t-contrast.

We estimated effect of working memory (2-back>0-back contrast) in each group. Then, from this contrast we created a union mask (uncorrected p-value 0.001). Within this union mask, we compared the effect of working memory across patient and control groups with whole brain mass univariate analysis (controls > NF1 patients contrast). Age and sex were included in the design matrix as covariates of no interest.

Volumes of Interest

Eight volumes of interest (VOIs) were defined in frontal and parietal lobes, based on existing meta-analysis of verbal and identity monitoring working memory (Emch et al., 2019; Owen et al., 2005). VOIs were defined as spheres with radius of 6mm, and they were additionally masked by the union mask of effect of working memory. This ensured that models reflect shared and unique patterns of neuronal activity related to working memory, rather than background activity. VOIs included bilateral superior parietal gyrus (SPG, MNI: -20, -56, 40; 20, -56, 50), bilateral ventrolateral prefrontal cortex (VLPFC, MNI: 32, 20, 4; -32, 24, 8), bilateral dorsolateral prefrontal cortex (DLPFC, MNI: -48, 16, 24; 48, 16, 24). Additionally, bilateral inferior parietal gyrus (IPG) was added based on peak working memory activation across all participants (MNI: -34, -44, 38; 36, -46, 40).

For every participant, the first eigenvariate of the timeseries of all voxels in each VOI was extracted and adjusted by F-contrast of main effects of the N-back task, which removed effects of motion and outlier scans from the timeseries.

Dynamic Causal Models

Once the time series of VOIs were extracted, DCM for fMRI was used to estimate the effective connectivity for each participant (Friston et al., 2003). Each model was fully connected and composed of 40 intrinsic and modulatory connections between the 8 VOIs. Based on the prior literature, the driving input entered IPG (Ma et al., 2011).

Following the inversion of first level DCMs, we performed second level-analysis using the parametric empirical Bayes (PEB) approach (Friston et al., 2016; Zeidman, Jafarian, Seghier, et al., 2019). The PEB analysis combines first-level DCMs and estimates the group-level GLM. This revealed the group mean connectivity shared across controls and patients, and the effect of NF1 diagnosis on connectivity, as well as estimating the between-subject variability. The PEB analysis was ran separately for A-matrix and B-matrix. We included age and sex as covariates of no interest and we mean-centred the whole design matrix.

Next, we investigated our hypothesis that the NF1 diagnosis would be associated with increased strength of inhibitory self-connections during working memory

in NF1 group (intrinsic connectivity in B-matrix). Therefore, we sequentially "switched off" self-connections of every region and compared model evidence between the full and reduced (nested) models, which differed only in their priors. To compare the models, we performed Bayesian model reduction (BMR), which derives the evidence and parameters of the reduced models from the full model and allows for Bayesian model comparison (BMC) using free energy of each model (Friston et al., 2016). Next, Bayesian model average was performed to obtain average of parameter values across models weighted by each model's posterior probability (Penny et al., 2007). The evidence level of the models is interpreted according to Kass and Raftery (1995). Finally, predictive validity of the model selected by BMR was tested with leave-one-out cross-validation. During validation, a PEB model was fitted to all but one participant and the diagnosis for the left-out participant was predicted. The PEB model fitted during cross-validation only included the intrinsic connections chosen by BMC. This was repeated until all participants had been left out.

Associations with behavioural performance

To explore the associations between patients' in-scanner working memory performance and DCM parameters, a series of Pearson's R tests was performed for the patient population. We provide the uncorrected p-values of the correlation coefficients. Accuracy was calculated for 2-back condition as number of correct responses out of the total number of trials (correct hits + correct omissions/number of trials). Response Time (RT) was calculated only for time to correct responses. Inverse efficiency score was defined as RT divided by accuracy.

Results

Mass Univariate Analysis

The effects of working memory (2-back>0-back contrast) were separately for patients and controls. Details of the local maxima are provided in Table 2 and Table 3 for controls and patients, respectively. Both groups showed bilateral activation related to working memory within the frontal regions including superior, middle, and inferior frontal gyri. Both groups showed activation in precentral gyri and supplementary motor area. Amongst parietal areas, both groups showed activation in IPG and precuneus. Other brain structures showing working memory effect included left insula and left globus pallidus.

Table 4 describes the local maxima of controls>patients contrast. Figure 1 illustrates the binarized mask of this contrast and the location of the VOIs. As hypothesized, the differences in activation included bilateral SPG and VLPFC, and left DLPFC. There was a relatively weak difference in activation of left IPG, left supramarginal gyrus and right angular gyrus. Differences in activation also extended over bilateral insula, left middle cingulate cortex, left calcarine fissure, left middle temporal gyrus, and right cerebellum.

Table 2 Whole brain mass univariate analysis: brain regions showing significant effects of working memory in neurotypical controls. Statistical threshold was set at family wise error corrected $p < 0.05$. Region labels were generated with Automated Anatomical Labelling 3 (Rolls et al., 2015).

cluster			peak				MNI			Label
p (FWE)	p (FDR)	cluster size (k)	p (FWE)	p (FDR)	T-value	Z-value	x	y	z	

0	0	272	0	0.065	10.12	6.19	42	-34	38	Supramarginal gyrus
			0.002	0.21	8.25	5.57	28	-56	40	Angular gyrus
			0.005	0.231	7.7	5.36	32	-52	46	Inferior parietal gyrus
0	0	256	0	0.15	8.98	5.83	-22	0	44	Superior frontal gyrus
			0.003	0.215	7.97	5.47	-20	4	66	Superior frontal gyrus,
			0.003	0.215	7.89	5.43	-26	2	56	Middle frontal gyrus
0	0	57	0.001	0.15	8.86	5.79	-2	6	58	Supplementary motor area
0	0	312	0.001	0.15	8.77	5.76	-28	-52	38	Inferior parietal gyrus
			0.002	0.215	8.04	5.49	-34	-52	50	Inferior parietal gyrus
			0.004	0.231	7.71	5.37	-30	-44	38	Inferior parietal gyrus
0	0	295	0.001	0.183	8.52	5.67	26	2	50	Superior parietal gyrus
			0.002	0.21	8.26	5.58	26	0	62	Superior parietal gyrus
			0.011	0.335	7.2	5.16	22	12	56	Superior parietal gyrus
0	0	74	0.002	0.215	8.06	5.5	-32	18	-2	Insula
0	0.008	30	0.003	0.215	7.9	5.44	18	-62	56	Superior parietal gyrus
0	0	93	0.003	0.215	7.87	5.43	6	14	48	Supplementary motor area
			0.006	0.267	7.57	5.31	-2	14	46	Supplementary motor area
0	0.02	21	0.008	0.296	7.36	5.23	32	18	-2	Lenticular nucleus, Putamen
0.004	0.141	8	0.009	0.296	7.35	5.22	46	-38	54	Inferior parietal gyrus
0	0.018	23	0.009	0.314	7.3	5.2	18	0	12	Caudate nucleus
0	0.019	22	0.011	0.335	7.23	5.17	-42	-4	28	Precentral gyrus
0.001	0.042	15	0.011	0.335	7.2	5.16	46	26	28	Inferior frontal gyrus, triangular part
0.001	0.033	17	0.018	0.471	6.95	5.05	8	-64	48	Precuneus
0.019	0.414	2	0.019	0.471	6.93	5.04	18	10	12	Caudate

										nucleus
0.008	0.255	5	0.024	0.589	6.78	4.98	-14	0	6	Lenticular nucleus, Pallidum
0.019	0.414	2	0.031	0.717	6.65	4.92	34	-68	40	Occipital
0.014	0.401	3	0.032	0.723	6.63	4.91	22	10	42	Superior frontal gyrus
0.019	0.414	2	0.034	0.732	6.61	4.9	-36	58	8	Middle frontal gyrus
0.019	0.414	2	0.035	0.749	6.59	4.89	-48	30	28	Inferior frontal gyrus, triangular part
0.019	0.414	2	0.039	0.818	6.53	4.86	36	-70	-28	Crus I of cerebellar hemisphere
0.027	0.541	1	0.045	0.917	6.46	4.83	-34	18	22	Inferior frontal gyrus, triangular part
0.027	0.541	1	0.049	0.984	6.41	4.81	-14	-6	16	Caudate nucleus

Table 3 Whole brain mass univariate analysis: brain regions showing significant effects of working memory in NF1 patients. Statistical threshold was set at family wise error corrected $p < 0.05$. Region labels were generated with Automated Anatomical Labelling 3 (Rolls et al., 2015).

cluster			peak				MNI			Label
p (FWE)	p (FDR)	cluster size (k)	p (FWE)	p (FDR)	T-value	Z-value	x	y	z	
0	0	505	0	0	10.18	7.11	28	0	50	Middle frontal gyrus
			0	0.019	7.65	5.97	32	2	60	Superior frontal gyrus, dorsolateral
0	0	858	0	0	9.9	7	-2	12	50	Supplementary motor area
			0	0.029	7.31	5.79	6	26	30	Middle cingulate & paracingulate gyri
			0.001	0.032	7.1	5.68	0	26	40	Superior frontal gyrus, medial
0	0	615	0	0.011	8.15	6.22	-36	-44	38	Inferior parietal gyrus
			0	0.016	7.92	6.1	-42	-50	46	Inferior parietal gyrus
			0	0.02	7.47	5.88	-	-	4	Inferior parietal gyrus

				2			30	58	8	
0	0	832	0	0.019	7.72	6.01	42	-44	50	Inferior parietal gyrus
			0	0.029	7.3	5.79	12	-70	54	Precuneus
			0.001	0.03	7.21	5.74	38	-46	42	Inferior parietal gyrus
0	0	113	0	0.019	7.67	5.98	-26	-60	-36	Lobule VI of cerebellar hemisphere
			0.003	0.104	6.55	5.37	-40	-70	-34	Crus I of cerebellar hemisphere
0	0	184	0	0.022	7.47	5.88	-46	18	36	Middle frontal gyrus
			0.001	0.03	7.21	5.74	-42	24	30	Inferior frontal gyrus, triangular part
			0.001	0.031	7.13	5.69	-46	30	34	Middle frontal gyrus
0	0	242	0.001	0.03	7.21	5.74	-24	0	54	Superior frontal gyrus, dorsolateral
			0.004	0.11	6.52	5.35	-28	6	60	Middle frontal gyrus
0	0	131	0.001	0.031	7.14	5.7	-46	16	0	Inferior frontal gyrus, opercular part
			0.001	0.044	6.95	5.6	-28	22	-4	Insula
			0.014	0.326	6.03	5.05	-42	20	-6	Inferior frontal gyrus, orbital part
0	0.002	47	0.001	0.031	7.14	5.7	-34	-2	38	Precentral gyrus
0	0	131	0.001	0.044	6.97	5.6	40	28	32	Middle frontal gyrus

0	0	67	0.002	0.066	6.75	5.48	34	20	-6	Insula
0.003	0.071	14	0.004	0.123	6.45	5.31	50	8	36	Precentral gyrus
0.004	0.103	11	0.013	0.317	6.05	5.07	-20	2	0	Lenticular nucleus, Pallidum
0.011	0.27	5	0.029	0.619	5.75	4.88	36	52	2	Middle frontal gyrus
0.017	0.388	3	0.03	0.62	5.74	4.87	-10	2	-2	Lenticular nucleus, Pallidum
0.022	0.469	2	0.034	0.69	5.69	4.84	26	46	-14	Anterior orbital gyrus
0.03	0.598	1	0.044	0.878	5.59	4.78	-18	6	10	Lenticular nucleus, Putamen

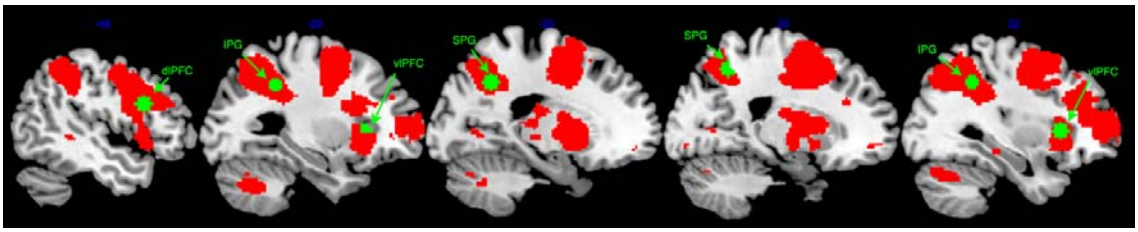

Figure 1 A binarized overlay of clusters generated by mass univariate analysis showing regions where controls have greater working memory related activation than NF1 patients. Green voxels illustrate the VOIs. The sagittal slices have the following coordinates: -48, -29, -20, 20, 32.

Table 4 Whole brain mass univariate analysis: brain regions greater working memory related activation in neurotypical controls than NF1 patients. Peak statistical threshold was uncorrected ($p < 0.001$). Region labels were generated with Automated Anatomical Labelling 3 (Rolls et al., 2015).

cluster			peak				MNI			Label
p (FWE)	p (FDR)	cluster size (k)	p (FWE)	p (FDR)	T-value	Z-value	x	y	z	
0.024	0.029	212	0.011	0.06	5.6	5.04	-18	-58	40	Middle occipital gyrus
0.009	0.016	265	0.082	0.233	4.97	4.56	20	-56	50	Superior parietal gyrus
			0.519	0.638	4.26	3.98	10	-64	48	Precuneus
0.08	0.08	146	0.16	0.31	4.74	4.38	-	2	1	Inferior frontal gyrus,

8			1	9			36	6	0	triangular part
			0.449	0.638	4.33	4.04	-34	18	12	Insula
			0.609	0.638	4.17	3.91	-26	24	0	Insula
0.001	0.002	435	0.573	0.638	4.2	3.94	-16	-68	6	Calcarine fissure and surrounding cortex
			0.819	0.734	3.95	3.72	-14	-52	-4	Lingual gyrus
			0.821	0.734	3.94	3.72	-14	-82	2	Lingual gyrus
0.811	0.646	34	0.584	0.638	4.19	3.93	-10	10	38	Middle cingulate & paracingulate gyri
0.533	0.402	59	0.71	0.734	4.07	3.82	22	-6	40	Middle cingulate & paracingulate gyri
0.901	0.698	25	0.755	0.734	4.02	3.79	-54	-48	14	Middle temporal gyrus
0.974	0.704	14	0.905	0.734	3.82	3.62	-24	46	12	Middle frontal gyrus
0.553	0.402	57	0.935	0.734	3.77	3.57	-38	4	22	Inferior frontal gyrus, opercular part
0.883	0.698	27	0.947	0.734	3.74	3.54	26	-58	2	Lingual gyrus
0.947	0.704	19	0.961	0.734	3.7	3.51	30	-32	-6	Hippocampus
0.991	0.746	9	0.963	0.734	3.69	3.5	32	-42	24	Angular gyrus
0.91	0.698	24	0.965	0.734	3.68	3.5	62	-38	18	Superior temporal gyrus
0.249	0.2	96	0.973	0.734	3.65	3.47	22	-74	-28	Crus I of cerebellar hemisphere

			0.983	0.734	3.6	3.43	30	-70	-26	Lobule VI of cerebellar hemisphere
0.986	0.704	11	0.974	0.734	3.65	3.47	32	26	8	Insula
0.974	0.704	14	0.98	0.734	3.62	3.44	-48	16	24	Inferior frontal gyrus, triangular part
0.979	0.704	13	0.981	0.734	3.62	3.44	16	-72	8	Calcarine fissure and surrounding cortex
0.959	0.704	17	0.986	0.734	3.58	3.41	-48	-36	30	Supramarginal gyrus
0.979	0.704	13	0.988	0.734	3.57	3.4	-26	6	44	Middle frontal gyrus
0.778	0.646	37	0.989	0.734	3.56	3.39	16	-94	0	Calcarine fissure and surrounding cortex
			0.994	0.754	3.51	3.35	16	-86	4	Calcarine fissure and surrounding cortex
0.954	0.704	18	0.99	0.734	3.55	3.38	20	-90	-8	Lingual gyrus
0.996	0.813	6	0.995	0.762	3.49	3.33	18	12	58	Superior frontal gyrus, dorsolateral
0.986	0.704	11	0.997	0.804	3.45	3.29	48	-38	24	Supramarginal gyrus
1	0.845	1	0.999	0.931	3.35	3.21	-12	10	56	Superior frontal gyrus, dorsolateral
0.995	0.798	7	0.999	0.931	3.35	3.2	-28	2	20	Supramarginal gyrus
1	0.845	1	0.999	0.938	3.34	3.19	-54	-6	44	Superior frontal gyrus, dorsolateral
0.999	0.845	3	1	0.963	3.31	3.17	4	-54	-32	Insula
0.999	0.845	2	1	0.974	3.29	3.15	-36	6	56	Postcentral gyrus

1	0.845	1	1	0.974	3.28	3.14	34	-48	50	Lobule IX of vermis
1	0.845	1	1	0.974	3.27	3.13	4	-66	-20	Middle frontal gyrus
1	0.845	1	1	0.974	3.25	3.12	-32	-38	32	Inferior parietal gyrus, excluding supramarginal and angular gyri
0.999	0.845	3	1	0.974	3.24	3.1	-8	-66	44	Precuneus
1	0.845	1	1	0.974	3.24	3.1	22	-32	8	Hippocampus
0.999	0.845	2	1	0.974	3.23	3.1	-34	-78	18	Middle occipital gyrus

Effective connectivity

Average connectivity

PEB model was fitted to the average connectivity of 0-back and 2-back conditions (A-matrix) to estimate the shared and unique connections across groups. [Figure] illustrates group mean connection strength and effect of NF1 diagnosis (whether it was associated with increase or decrease to connection strength). Here, we focus on group differences that have strong evidence (posterior probability of including the connection in the model >0.95%). In patients, relative to controls, there was stronger intrinsic connectivity in all regions of left hemisphere and right vlPFC. Across hemispheres, parietal regions (both IPG and SPG) shared stronger cross-hemispheric connections to their contralateral counterparts. Focusing on left hemisphere, left dlPFC projected weaker connections to SPG and right dlPFC, but stronger connection to vlPFC. Left IPG projected weaker connections to SPG and vlPFC. Connection from left IPG to SPG was weaker. In addition, left IPG had weaker connection to vlPFC, but also IPG received stronger connection from vlPFC. Finally, in right hemisphere, right dlPFC projected weaker connections to IPG and SPG, but exchanged stronger connections with vlPFC. In parietal regions right SPG sent stronger connection to IPG.

Figure 2 Average connectivity during the N-back task (0-back and 2-back conditions) in neurotypical and NF1-diagnosed adolescents (left) and group differences (right). All non-zero connections have passed the 95% posterior probability threshold for being included in the model.

Modulatory connectivity

The PEB model was separately fitted to modulatory effect of working memory (B-matrix). Again, we focus on strong evidence for group differences. In patients, working memory evoked weaker intrinsic connectivity of left dlPFC, weaker connection strength from left IPG to right IPG and left vlPFC, and stronger connection from right IPG to right dlPFC and from right SPG to left SPG.

Figure 3 Modulatory connectivity in neurotypical and NF1-diagnosed adolescents (left) and group differences (right). All non-zero connections have passed the 95% posterior probability threshold that parameter is >0.

BMR was conducted to test the hypothesis that these differences were driven by intrinsic connectivity. The winning model according to BMC had a posterior probability (Ppost) of 0.34%. It suggested that NF1 patients have stronger intrinsic connectivity of left vlPFC (Ppost = 52%), and weaker connectivity of right vlPFC (Ppost = 52%) and left dlPFC (Ppost = 89%). The parameters of these connections were weakly predictive of NF1 diagnosis; correlation coefficient between true and predictive scores was 0.19 (p = 0.055).

Associations with behaviour

There was no correlation between intrinsic connectivity of left dlPFC or bilateral vlPFC and accuracy or response times.

Discussion

In this work, we investigated if NF1 participants have greater inhibitory activity in frontoparietal network related to verbal working memory than neurotypical controls. By implementing DCM analysis, we demonstrated that group differences during working memory are driven by more inhibitory intrinsic connectivity of left dlPFC and left vlPFC, and less inhibitory intrinsic connectivity of right vlPFC. During leave-one-out cross-validation, these patterns were somewhat predictive of group allegiance (control/NF1). However, we also observed that average connectivity (i.e. average of 0-back and 2-back) of left dlPFC, IPG, SPG and bilateral vlPFC was increased in NF1, suggesting greater overall sensitivity of these regions to inputs. Importantly, this discrepancy between average and modulatory connectivity suggests that overall NF1 participants are responsive to cognitive task-related inputs but may be less able to adapt to the task demands of working memory.

To study working memory differences, we selected frontal and parietal regions that showed activity related to working memory in both groups. A meta-analysis has related the activity of these regions was related to identity monitoring of verbal stimuli (Owen et al., 2005). In addition, these regions showed reduced BOLD activity in response to working memory demands in NF1 participants than controls, and this echoed previous NF1 literature (Ibrahim et al., 2017; Shilyansky et al., 2010). Surprisingly, the DCM analysis of these regions revealed an unexpected finding that NF1 participants had stronger intrinsic average connectivity (i.e. A-matrix reflecting average connectivity during 0-back and 2-back conditions). In DCM, intrinsic connectivity reflects the sensitivity of the region to inputs, where stronger intrinsic connectivity suggests more inhibition of input-related signals (Snyder et al., 2021). Therefore, higher average connectivity suggests that NF1 group maintains an active frontoparietal network. This stronger average connectivity in left dlPFC, IPG, SPG, and bilateral vlPFC may reflect greater recruitment of neural processing to perform the N-back task. This interpretation is consistent with neural efficiency hypothesis that neurodivergent individuals compensate/adapt to their condition through greater neural engagement for equivalent performance (Neubauer & Fink, 2009). Similar compensatory engagement of neural resources has been noted in autism spectrum conditions and attention deficit/hyperactivity disorder, where Supekar et al. (2013) found greater functional connectivity in prefrontal-subcortical loop during working memory, and Cortese et al. (2012) found greater connectivity in frontoparietal networks during cognitive control tasks. Together, these findings point to a shared compensatory mechanism across developmental conditions that maintains cognitive performance. Specifically, atypical developmental trajectories, may lead to increased neural engagement for basic task completion.

However, Poldrack (2015) raises an important point that observed differences may be indicative of different cognitive processes, different neural computations, differences in neural firing intensity/duration, or true metabolic efficiency differences. Here, our implementation of DCM method becomes particularly useful in addressing this ambiguity because it estimates both average and modulatory connectivity (A-matrix and B-matrix respectively). While average connectivity was increased for NF1 in response to N-back task, modulatory connectivity showed more inhibitory intrinsic connectivity in left dlPFC and left vlPFC, but less inhibitory intrinsic connectivity in right vlPFC compared to controls. Previous research indicates that there is left-lateralised specialisation of verbal working memory due to engagement of phonological rehearsal (Crottaz-Herbette et al., 2004; Emch et al., 2019; Walter et al., 2003). Therefore, increased inhibitory modulation in left prefrontal regions suggests reduced verbal processing during high working memory demands. This indicates that despite greater average connectivity, NF1 participants do not adapt their processing to verbal working memory demands. We hypothesize that this may occur due to high engagement of neural resources at baseline creating a ceiling effect, where it becomes more difficult to adapt further to higher cognitive demands of more demanding tasks, such as tasks requiring higher working memory, inhibit control, task switching etc.

We can further make sense of these differences in cognitive processing between NF1 and controls by considering the cognitive role of individual regions in the fronto-parietal network. Overall, individual studies and meta-analysis show that that dlPFC is involved with executive function, working memory, cognitive control, and attention (Jimura et al., 2018; Kim et al., 2015; Osaka et al., 2003; Owen et al., 2005; Rottschy et al., 2012; Vartanian et al., 2013; Wager & Smith, 2003; Yaple et al., 2019). Further, it has been proposed that dlPFC supports monitoring of stimulus, selection of responses under working memory and

attentional demands (Bichot et al., 2015; Rowe et al., 2000). Further adding to this argument, Huey et al. (2016) proposed that left dlPFC is involved with monitoring of individual stimuli or events, whereas the right dlPFC is involved with integration of information across events. Importantly, working memory deficits in NF1 patients have been linked to hypoactivity of left dlPFC (Ibrahim et al., 2017; Shilyansky et al., 2010). Here we further add to these results the finding that this hypoactivity is related increased inhibitory intrinsic connectivity. Additionally, it may be related to diminished ability to adapt to working memory demands and allocate neural resources. Additionally, we found increased inhibitory intrinsic connectivity of left vlPFC, which modulates phonological processing (Owen et al., 2005; Walter et al., 2003). This further reinforces the possibility of diminished phonological processes. Meanwhile, the right vlPFC has been related to inhibitory control, attention regulation, and filtering of distractors (Aron et al., 2014; Hampshire et al., 2010; Shanmugan et al., 2016). This suggests that NF1 group has reduced filtering of task-irrelevant, possibly old, stimuli. To summarise, NF1 group's working memory performance appears to be affected by reduced phonological processing and increased interference from distractors and irrelevant stimuli entering the working memory systems.

It is important to understand this discussion in the context of methodological limitations of our analysis. The DCM analysis produces models of interactions between a set of neurological populations. This means that other neuronal populations, outside the set of chosen VOIs also likely contribute to the dynamics of the regions we choose to study. In other words, the hypoactivity reported here is limited to the context of processes of frontoparietal networks. To illustrate, we explored in this analysis how working memory inputs enter, how they are maintained and manipulated, but we cannot comment on other processes such as inhibitory control, attentional processing, early visual processes or motor processing. Each of these components is a subject of its own study and offers opportunities for future research. Additionally, it is important to note that NF1 participants were not off their regular medications that may influence their cognitive processing. We did not include either medication status in the PEB analysis, nor comorbid diagnosis with over neurodevelopmental conditions.

Overall, this work demonstrates that NF1 participants have increased average intrinsic connectivity in many working-memory related regions, which suggests underlying compensatory mechanisms of increased neural activity to achieve baseline cognitive tasks. However, the modulatory intrinsic connectivity revealed reduced phonological processing (left dlPFC and vlPFC inhibition) and reduced filtering processes (right vlPFC disinhibition), which suggests that NF1 group has difficulty to adapt to higher task demands.

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