Mega-analysis of structural magnetic resonance imaging in 493 patients with functional neurological disorder

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Background

Despite a resurgence of research interest in functional neurological disorder (FND), its pathophysiology remains poorly understood. Structural neuroimaging studies have typically been underpowered and have produced heterogenous findings.[1] Mega-analyses combine individual patient data from multiple studies, substantially increasing statistical power.[2] We utilised this method to probe the complex pathophysiology of FND.

Methods

Collaboration

In this FND Society Neuroimaging Committee study, international research groups with MRI data of functional motor or seizure patients and healthy controls were invited to send T1-weighted images and associated clinical variables.

MRI data pre-processing, extraction, and harmonisation

Data was pre-processed with Freesurfer 6.0.0; the standard recon-all procedure was used to estimate cortical thickness, subcortical volumes, and surface area morphometrics based on the Destrieux atlas. Manual checks for outliers were used to identify possible errors in the white-grey matter boundary and pial reconstruction steps; 23 patient and 30 controls with insufficient quality or missing demographics were discarded. We used the ComBat harmonisation method, an empirical Bayesian algorithm, to minimise variance due to the scanners used across sites.[3]

Analysis

Initial ANOVAs corrected for multiple comparisons was used to select regions of interest (ROI) for cortical thickness & surface area and subcortical volumes. Cohorts were then compared with ROI MANCOVAs adjusted for age, sex, & total intracranial volume.

Clinical correlation

Dichotomised variables for depression, anxiety, antidepressant use, and length of illness were available for 62.1% of the FND cohort. Patients with/without were compared with adjusted MANCOVAs.

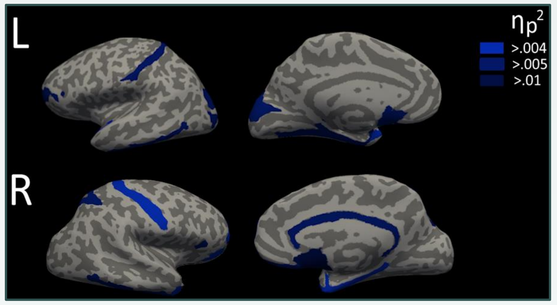
Results

The dataset consisted of 564 age- and sex-matched controls and 493 patients; some had both subtypes (overall 314 motor, 193 seizures).

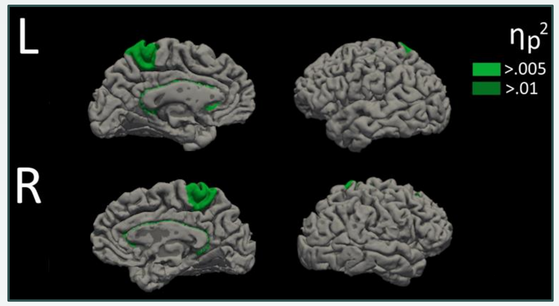
	n	Age			Sex			
		Mean	SD	p	Female	Male	Chi^2	p
Controls	564	38.1	12.7	0.88	402 (71.3%)	162	2.3	0.1
FND	493	38.2	12.7		372 (75.5%)	121		

Group level differences

The FND cohort showed **reduced cortical thickness** in regions including the *bilateral* paracentral gyri and sulci, superior precentral sulci, and superior frontal sulci; **reduced cortical surface area** in varying fontal, occipital, & temporal regions; **reduced volumes** in regions including the *bilateral* putamen & hippocampi. In each case, the differences were small (η_p^2 **<0.016**). Significant regions survived leave-one-out analysis.



Cortical surface area

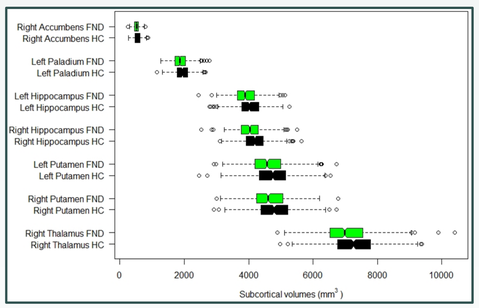


Cortical thickness

Clinical correlation

Depression: ↓ thickness in *bilateral* superior precentral sulci, *left* superior frontal gyrus & *right* superior frontal sulcus; ↓ surface area in the *left* parahippocampal gyrus and *right* subcallosal gyrus. No differences in subcortical volumes were found.

Anxiety, antidepressant use and length of illness: No significant differences were identified.



Subcortical volumes

Subgroup analyses

Functional motor disorder

- *Cortical thickness:* ↓ in 9 regions including the *bilateral* paracentral sulci and gyri, precentral sulci, and superior frontal sulci.
- *Surface area:* ↓ in 26 regions including the *bilateral* olfactory sulci, *left* postcentral gyrus, *right* subcallosal gyrus and superior parietal gyrus.
- *Subcortical volumes:* ↓ *bilaterally* in hippocampi, putamen, thalami ↓ unilaterally in *left* palladium.

Functional seizures

- *Cortical thickness:* ↓ in *left* paracentral gyrus & sulcus, superior frontal gyrus & sulcus and *right* cuneal gyrus, precentral gyrus, & superior precentral sulcus. ↑ *bilaterally* in pericallosal sulci.
- *Surface area:* ↓ cortical surface area in 19 regions including the bilateral subcallosal gyri, left frontamarginal sulcus and gyrus and inferior temporal sulcus, right pericallosal sulcus.
- *Subcortical volumes:* ↓ in *right* nucleus accumbens.

Discussion

This mega-analysis represents the largest structural imaging study in FND to date. Results suggest FND is associated with small reductions in cortical thickness, surface area, and volumes.

Regions affected

FND was associated with reduced cortical thickness in frontal and motor regions, which may be associated with planning and execution of movement; thickness was increased in the pericallosal sulci, part of the limbic system, which may suggest an affective contribution. Surface area was reduced in multiple areas, particularly in orbitofrontal, limbic, and temporal regions.

Cause or effect?

Cortical thickness and surface area are considered orthogonal components affected by distinct underlying processes.[4] Future research could investigate the aetiological significance of these findings, and whether they are specific to FND.

Future directions

Further granular analysis, for example via receptor density mapping, could further elucidate the pathophysiology of this disabling disorder. Consensus regarding the minimum clinical variables to collect in future FND research is encouraged.

Contributing groups

King's College London, University of Alabama at Birmingham, Lurija Institute for Rehabilitation and Health Sciences, National Institute of Neurological Disorders and Stroke, Maastricht University Medical Center, University Medical Center Groningen, University of Brescia, University of Belgrade, Charles University Prague, Masaryk University, National Center of Neurology and Psychiatry Japan, University of California Los Angeles, Ruhr University Bochum, Massachusetts General Hospital, Insel Gruppe Ag Inselspital.

References

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