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Identifying motor functional neurological disorder using resting-state functional connectivity

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ABSTRACT

Background: Motor functional neurological disorder (mFND) is a clinical diagnosis with reliable features; however, patients are reluctant to accept the diagnosis and physicians themselves bear doubts on potential misdiagnoses. The identification of a positive biomarker could help limiting unnecessary costs of multiple referrals and investigations, thus promoting early diagnosis and allowing early engagement in appropriate therapy.

Objectives: To test whether resting-state (RS) functional magnetic resonance imaging could discriminate patients suffering from mFND from healthy controls.

Methods: We classified 23 mFND patients and 25 age- and gender-matched healthy controls based on whole-brain RS functional connectivity (FC) data, using a support vector machine classifier and the standard Automated Anatomic Labeling (AAL) atlas, as well as two additional atlases for validation.

Results: Accuracy, specificity and sensitivity were over 68% ($p = 0.004$) to discriminate between mFND patients and controls, with consistent findings between the three tested atlases. The most discriminative connections comprised the right caudate, amygdala, prefrontal and sensorimotor regions. Post-hoc seed connectivity analyses showed that these regions were hyperconnected in patients compared to controls.

Conclusions: The good accuracy to discriminate patients from controls suggests that RS FC could be used as a biomarker with high diagnostic value in future clinical practice to identify mFND patients at the individual level.

1. Introduction

Motor functional neurological disorder (mFND) – formerly called "hysteria" – represents a clinical diagnosis for which positive bedside signs exist (Daum et al., 2014), and treating clinicians, mostly neurologists and psychiatrists, can refer to established diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM-5)). Even though misdiagnosis rates are low (Stone et al., 2009), neurologists still fear missing an underlying organic pathology (Slater, 1965) and a majority continue to engage in an exclusionary process involving many additional investigations (Espay et al., 2009). A misdiagnosis in the other direction – i.e., diagnosing an organic disease when the actual diagnosis is mFND – can also have serious consequences for the patients as this results in unnecessary treatments such as thrombolysis (Vroomen et al., 2008). Appropriate therapy is then delayed, which importantly impacts outcome (Gelauff et al., 2014) and societal costs (Carson et al., 2011).

Besides the fear of misdiagnosis, neurologists avoid discussing the diagnosis of functional neurological disorder (FND) with their patients (Kanaan et al., 2009a) because they themselves bear doubts about an alternate explanation for the symptoms of feigning (Kanaan et al., 2009b). Patients in turn feel their doctors do not understand them, which leads to multiple consultations for the same symptoms and change of general practitioner (Crimlisk et al., 2000). The identification of a positive biomarker for mFND could strengthen the physician's clinical diagnosis and reassure the patients, thus limiting unnecessary costs of multiple referrals and investigations, promoting an early diagnosis and allowing early engagement in appropriate therapy.

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A new and promising tool in the search of biomarkers for neuropsychiatric disorders is resting-state (RS) functional magnetic resonance imaging (fMRI) (Woodward and Cascio, 2015) which allows the study of blood oxygen level dependent (BOLD) signal fluctuations generated under resting conditions. The temporal correlation between the time courses of different brain regions is computed to obtain measures of functional connectivity (FC). Compared to active tasks, the advantage of RS fMRI is that behavioral differences between patients and controls have lower impact on the interpretation of the results.

Literature in functional neuroimaging of mFND has been dominated by task-based studies, all aiming at uncovering the neural correlates of the disorder. Two RS studies in mFND patients (Maurer et al., 2016; Baek et al., 2017) have investigated neural correlates of the disorder but no studies to date have used a multivariate classification approach to investigate RS FC as a potential positive biomarker. The aim of our study was therefore to use whole-brain RS FC in a predictive setting to discriminate mFND patients from healthy controls.

2. Methods and materials

2.1. Participants

53 subjects (26 mFND patients and 27 controls matched for age and gender) participated in the study (Table 1). Three patients (1 patient with movement disorders and 2 patients with weakness) and 2 healthy controls were excluded from analysis due to excessive movement in the scanner, resulting in a total sample of 48 subjects. Patients were recruited from the outpatient clinic of a tertiary university hospital (University Hospitals Geneva, Department of Clinical Neurosciences). Two board-certified neurologists (SG or SA) confirmed the diagnosis of FND according to DSM-5 criteria and using motor positive signs (e.g., Hoover sign or tremor variability, distractibility and entrainment test). Healthy control subjects (with a similar sociodemographic background and individually matched to the patients by age and sex) were recruited via advertisement. For both groups, the main exclusion criteria were current neurological disorders, substance dependence and contraindications for MRI scanning. The study was approved by the ethics committee of the University Hospitals of Geneva (CER 14-088). All participants gave written informed consent in accordance with the Declaration of Helsinki.

2.2. Data acquisition

2.2.1. Clinical evaluation

Participants completed the State Anxiety Inventory (STAI-S) (CDG et al., 1983) and the Beck Depression Inventory (BDI) (Beck et al., 1996) on the day of MRI session. Clinical severity of the motor symptom was evaluated by the neurologists with a 0–5 Clinical Global Impression Score (CGI) (0 = no symptom to 5 = very disabling symptom).

Table 1
Demographic values and clinical scores.

	mFND patients (n = 23)	Healthy controls (n = 25)	P-value
Age, mean (SD), years	42.4 (13.9)	42.4 (13.0)	0.985
Gender (females/males)	21/2	22/3	0.708
Type of symptom	11 weakness 12 tremor/jerks/dystonia	NA	
Disease severity (median CGI)	2	NA	
Disease duration, mean (SD), months	4.8 (6.3)	NA	
BDI score, mean (SD)	7.5 (5.2)	1.9 (6.1)	< 0.001[a]
STAI-S score, mean (SD)	34.8 (9.4)	34(8.1)	0.940

STAI-S: Anxiety State value, BDI: Beck Depression Index, CGI: Clinical Global Impression.
SD = standard deviation; *NA = not applicable.*
[a] Significantly different between groups.

2.2.2. MRI acquisition parameters

MRI was performed using a 3.0 Tesla unit (Siemens, Magnetom TrioTim). Functional imaging data and one structural image were acquired in one session. fMRI data were acquired using a whole-brain single shot multi-slice BOLD echo-planar-imaging (EPI) sequence with the following parameters: TR: 2 s; TE: 20 ms; flip angle 80°; PAT factor = 2; FOV: 240 mm; matrix size: 64 × 64 × 40; 2.5 mm slice thickness; interslice gap 1.1125 mm; voxel size 3.00 × 3.00 × 2.50 mm; TA: 5:08 min, 150 functional images.

During the RS fMRI session, the subjects were instructed to lie still, to think of nothing in particular and to watch a cross symbol projected on a black screen. The scan protocol for structural MRI consisted of a T1-weighted MPRAGE sequence with the following parameters: TR: 1.9 s; TE: 2.27 ms; flip angle = 9°; PAT factor = 2, voxel size 1.0 × 1.0 × 1.0 mm; acquisition time: 5:04.

2.3. Data analyses

Demographic and clinical data were compared between the two groups with two-sample *t*-tests or Mann-Whitney *U* tests (depending on the distribution normality), and the chi2 test when appropriate.

2.3.1. Preprocessing of imaging data

For preprocessing, we relied on a previously used pipeline (Richiardi et al., 2012) using SPM12 tools (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were first realigned, then the mean functional image was co-registered with the structural image. The latter was segmented into grey matter, white matter, and cerebrospinal fluid. A customized version of the IBASPM toolbox (Aleman-Gomez et al., 2006) was used to build an individual structural brain atlas, based on the AAL atlas (Tzourio-Mazoyer et al., 2002). In order to check the consistency of the results, two other atlases, the Hammers probabilistic structural atlas (Hammers et al., 2003), and the Shirer functional atlas (Shirer et al., 2012), were additionally chosen for comparison. The atlas was then mapped back onto the native resolution of the functional data, and region-averaged time series were extracted. The first 10 time points were discarded to ensure magnetization equilibrium. Motion parameters, as well as the average signal of a mask of white matter and cerebrospinal fluid, were regressed out. Time series were Winsorized to the 95th percentile to increase robustness to outliers (e.g., spikes). Time courses were then filtered into frequency subbands using a wavelet transform (cubic orthogonal B-spline wavelets). Five frequency subbands were extracted, respectively with main bandpass characteristics at 0.5–1 Hz, 0.25–0.5 Hz, 0.125–0.25 Hz, 0.0625–0.125 Hz, and 0.0312–0.0625 Hz. We investigated alterations of FC in the latter subband (0.0312–0.0625 Hz), as this subband represents typical low-frequency RS fluctuations. Motion-related artefacts were accounted for as described in Supplemental File Appendix 1.

2.3.2. RS FC modelling and classification

We computed pairwise Pearson correlation coefficients between all atlas regions in order to obtain a correlation matrix (number of regions × number of regions) for each subject (see Supplemental File, Appendix 2). Next, we converted the correlation coefficients to z-scores using Fisher-Z transformation, and used them as features for the classifier by reshaping the upper-triangular part of the matrix (excluding the diagonal) as a vector.

We used a linear Support Vector Machine (SVM) classifier with L2 regularization to learn a discriminant function that would optimally separate the two groups. The SVM is a supervised learning method that performs binary classification, by building the largest-margin hyperplane allowing for an optimal separation of the training examples. We