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Corticolimbic Fast-Tracking: Enhanced Multimodal Integration in Functional Neurological Disorder

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Abstract

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All other authors report no conflicts of interest.

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Objective: Some individuals with functional neurological disorder (FND) exhibit motor and affective disturbances, along with limbic hyper-reactivity and enhanced motor-limbic connectivity. Given that the multimodal integration network (insula, dorsal cingulate, temporoparietal junction (TPJ)) is implicated in convergent sensorimotor, affective and interoceptive processing, we hypothesized that patients with FND would exhibit altered motor and amygdalar resting-state propagation to this network. Patient-reported symptom severity and clinical outcome were also hypothesized to map onto multimodal integration areas.

Methods: Between-group differences in primary motor and amygdalar sub-nuclei (laterobasal, centromedial) were examined using graph-theory stepwise functional connectivity (SFC) in 30 patients with motor FND compared to 30 healthy controls. Within-group analyses correlated functional propagation profiles with symptom severity and prospectively collected 6-month outcomes as measured by a Screening for Somatoform Symptoms Conversion Disorder subscale and Patient Health Questionnaire-15 composite score. Findings were cluster-wise corrected for multiple comparisons.

Results: Compared to controls, patients with FND exhibited increased SFC from motor regions to the bilateral posterior insula, TPJ, middle cingulate cortex, and putamen. From the right laterobasal amygdala, the FND cohort showed enhanced connectivity to the left anterior insula, periaqueductal gray and hypothalamus among other areas. In within-group analyses, symptom severity correlated with enhanced SFC from the left anterior insula to the right anterior insula and TPJ; increased SFC from the left centromedial amygdala to the right anterior insula correlated with clinical improvement. Within-group associations held controlling for depression, anxiety and antidepressant use.

Conclusions: These neuroimaging findings suggest potential candidate neurocircuit pathways in the pathophysiology of FND.

Keywords

conversion disorder; somatization; psychogenic nonepileptic seizures; functional movement disorders; fMRI

INTRODUCTION

Despite its important role in the development of modern-day neurology and psychiatry, functional neurological disorder (FND, a.k.a. conversion disorder) has been largely neglected by both fields for decades.[1,2] However, the reframing of FND as a “rule-in” diagnosis based on neurological signs and semiologic features has catalyzed renewed interest.[3,4] Improved diagnostic specificity offers the opportunity to elucidate the pathophysiology of this enigmatic condition, which in turn, could challenge mind-body dualism, reduce patient stigma, and aid the development of neurobiologically-informed treatments.

Several neuroimaging studies in FND cohorts have identified amygdalar abnormalities including hyper-reactivity to affectively-valenced stimuli,[5–8] impaired habituation,[7] sensitized emotional processing,[5] and heightened coupling to motor preparation areas including the supplementary motor area (SMA).[6,7,9,10] For example, patients with FND

performing an affectively-valenced face viewing task demonstrated increased amygdalar activity and delayed habituation compared to controls.[7] These findings were replicated in another FND study that also showed increased dorsal anterior cingulate cortex (ACC), periaqueductal gray (PAG) and SMA activations during emotional processing in patients compared to controls.[5] Increased task-based[67] and resting-state[811] amygdalar coupling to motor and cognitive control regions has also been described. In addition, cingulo-insular resting-state connectivity to sensorimotor areas is increased in some FND populations,[12] and these connectivity relationships correlate with symptom severity.[13] While important unanswered questions remain, such as the role of specific amygdalar sub-nuclei, these findings support salience network (amygdala, cingulo-insular, PAG) involvement in the pathophysiology of FND.

Neuroimaging findings related to altered motor preparation, execution, inhibitory control and conceptualization have also been reported in patients with FND.[14–16] For example, patients with functional paralysis attempting to move an affected limb exhibited an expanded network of insular, ventrolateral prefrontal cortex, basal ganglia and lingual gyrus activations.[17] During the execution of internally generated movements in individuals with functional movement disorders, similar anterior insular and amygdalar hyperactivations were observed.[18] Amplified startle responses have also been described in individuals with FND.[19] While heightened limbic-paralimbic influence on behavior has been proposed as an important aspect of the pathophysiology of FND,[7] the specific pathways through which motor and affective neural systems interact in FND remain poorly understood.

Stepwise functional connectivity (SFC) is a novel graph-theory resting-state functional connectivity approach developed by Sepulcre and colleagues that characterizes the propagation and convergence of functional connectivity across brain networks.[20–22] Conventional resting-state methods predominantly characterize the segregation of discrete large-scale networks; SFC is specifically designed to capture not only the segregation of brain networks but also the integration between them, as a proxy of the information flow across neuronal systems. Using this method, sensorimotor systems in healthy subjects have been observed to propagate over a series of functional connectivity relay stations (link-steps) to a core set of multimodal integration areas[2021]. The multimodal integration network includes the anterior insula, dorsal ACC/middle cingulate cortex (MCC), ventral premotor cortex, and temporoparietal junction (TPJ). Anterior portions of the multimodal integration network overlap with the salience network, while posterior areas of this network (e.g., TPJ) are implicated in motor intention awareness and action authorship deficits in FND.[23–25] Notably, SFC has characterized mechanistic insights in neurologic[26] and neuropsychiatric populations.[27]

In this resting-state neuroimaging study, we examined the functional propagation of primary motor (hand, foot, tongue) and amygdalar (laterobasal, centromedial nuclei) regions in 30 patients with motor FND compared to 30 healthy controls. A SFC interconnector analysis also explored common points of altered functional connectivity between motor and amygdalar areas in patients with FND compared to controls. Complementary within-group approaches investigated correlations between SFC profiles, patient-reported symptom severity, and 6-month clinical outcomes. We have previously characterized salience network

structural alterations in this cohort,[28,29] and have theorized that cingulo-insular areas contribute to impaired integration of sensorimotor, affective and viscerosomatic information in FND populations.[30] Thus, we hypothesized that individuals with motor FND would exhibit altered motor and amygdalar link-step connectivity to the multimodal integration network. We also hypothesized that FND symptom severity and prospectively collected 6-month clinical outcome would correlate with multimodal integration network functional connectivity profiles.

METHODS

Adapted from references.[20–22]

Participants and questionnaires

All subjects signed informed consent and the Partners Human Research Committee approved this study. Thirty subjects with motor FND (24 women, 6 men; mean age=40.1±12.9; average illness duration=3.0±3.8 years; 24-right-handed, 6-ambidextrous or left-handed) were recruited from the Massachusetts General Hospital FND Clinic following a “rule-in” FND diagnosis in accord with the Diagnostic and Statistical Manual of Mental Disorders 5th Edition criteria.[3] An additional 5 patients were enrolled but excluded following imaging preprocessing (see Supplementary Methods). Given the overlap across the motor FND spectrum,[30] we used a transdiagnostic approach that included those with clinically-established functional movement disorders (n=16),[31] functional weakness (n=12),[32] and documented (n=12) or clinically-established (n=1) psychogenic nonepileptic seizures (PNES).[33] Ten of the 30 subjects had mixed motor FND. Exclusion criteria included major neurological comorbidities with magnetic resonance imaging (MRI) abnormalities, epilepsy, poorly controlled medical problems with known central nervous system consequences, active substance dependence, a history of mania or psychosis, and/or active suicidality. Comorbid psychiatric diagnoses as assessed using the Structured Clinical Interview (SCID-I) for DSM-IV-TR were present in 27 of 30 participants. Fourteen patients were on selective serotonin reuptake inhibitors (SSRIs) and/or serotonin-norepinephrine reuptake inhibitors (SNRIs). See Supplementary Table 1 for clinical information. Thirty healthy subjects (22 women, 8 men; mean age=40.0±12.6; 25-right-handed, 5-ambidextrous or left-handed) were recruited through local advertisements, and all screened negative for SCID-I major psychiatric comorbidities (one control met criteria for past depression not-otherwise-specified). Five additional controls were enrolled but excluded due to lifetime major psychiatric comorbidities (n=4) or excess head motion (n=1).

Subjects completed the Conversion Disorder subscale of the Screening for Somatoform Symptoms-7 scale (SOMS:CD)[34] and the Patient Health Questionnaire-15 (PHQ15)[35] as patient-reported symptom severity measures within a detailed psychometric battery at enrollment. The SOMS:CD is a 14-item measure of sensorimotor FND symptoms within the past 7 days, with each item scored on a 5-point scale. The PHQ15 is a 15-item measure of somatic complaints within the past 4 weeks, with each item scored on a 3-point scale. These scales were also prospectively completed at 6-month follow-up by 22 of 30 patients (8 were lost to follow-up; interval follow-up=6.1±1.1 months). To reduce multiple comparisons, we

constructed a SOMS:CD-PHQ15 composite by averaging the z-scores of the two variables. All subjects also completed the Beck Depression Inventory-II and the Spielberger State-Trait Anxiety Inventory (STAI).

Prior to enrollment, patients were diagnosed with FND and the term "Functional Neurological Disorder" was communicated along with the pertinent motor-subtype.[36] FND was presented as common, real, and treatable. Patients were introduced to the www.neurosymptoms.org website and given printed educational materials. Treatments were individualized, emphasizing cognitive behavioral therapy (CBT) and physiotherapy (PT). Fifteen individuals were in psychotherapy at baseline and 8 were newly referred (including one who remained in supportive psychotherapy while also starting CBT). In CBT, patients were encouraged to explore the relationships between functional symptoms, thoughts, behaviors, emotions and psychosocial factors.[37] Nine were in PT at baseline, and 5 were newly referred. Physiotherapists were recommended to use the Nielsen et al recommendations.[38] Patients did not exclusively receive care at MGH, which limited compliance information.

MRI data acquisition and preprocessing

See Supplementary Methods for data acquisition and preprocessing procedures including scrubbing head motion correction.

Stepwise functional connectivity analyses

SFC methods delineated the functional propagation of specific regions-of-interest (ROIs) across distinct link-steps.[20–22] First, individual connectivity matrices were computed. As shown in Fig. 1, the Pearson correlation between the time series of all pairs of cortical-subcortical gray matter voxels were computed. Then, a Fisher transformation was applied to the resulting correlation matrix. After removing negative values due to their controversial interpretation, a false discovery rate correction of p=0.0001 was applied to obtain only the most significant links. Thus, a high-resolution 5142 × 5142 connectivity matrix was obtained for each subject.

Validated bilateral Montreal Neurological Institute (MNI) voxel-wise hand (±41, −20, 62), foot (±6,−26,76), and tongue (±55,−4,26) primary motor cortex ROIs were chosen.[39] In addition, laterobasal and centromedial amygdalar ROIs were extracted from the probabilistic cytoarchitectonic mapping of the human amygdala in the SPM anatomy toolbox consistent with previously validated approaches[40] (Fig. 1 and Supplementary Fig. 1). Only 3 link-steps are presented given that healthy subjects reach the multimodal integration network by this stage.[2021]

Between-group analyses

Two-class general linear models examined between-group differences in the stepwise functional propagation of motor and amygdalar areas. All analyses (including within-group analyses described below) controlled for age, gender, and handedness (right-handed yes/no). Secondary analyses also adjusted between-group findings for depression and anxiety scores. There were no group-level differences in mean frame displacement (FND: 0.098±0.055;

controls: 0.08±0.043; p-value=0.15). Between-group SFC findings were corrected for multiple comparisons using Monte Carlo simulation cluster-wise correction with 10,000 iterations to estimate the probability of false positive clusters with a p-value<0.05.

Exploratory between-group interconnector analysis

While SFC delineates functional connectivity pathways from one region to the rest of the brain, it is not well suited to delineate interconnecting paths across multiple ROIs. Interconnector analysis, another graph-theory network analysis,[2141] restricts the SFC analysis only to those pathways that end in a common target. Following the identification of between-group SFC differences from *a priori* ROIs (see results), statistically significant motor and amygdalar ROIs were used in a single interconnector analysis to test for common sites of altered functional propagation. For this exploratory general linear model analysis, a right-tailed uncorrected t-test was used to compute group differences between patients and controls. Only clusters larger than 1.080 mm^3 with a $p<0.05$ were reported to minimize Type-I errors.

Within-group correlation with symptom severity

A single-class general linear model investigated the effect of symptom severity (SOMS:CD-PHQ15 composite). There was no significant relationship between individual subject frame displacements and composite scores (Spearman correlation 0.24; p-value=0.2). The motor and amygdalar ROIs used for between-group analyses were also used here (although no significant results were identified). We also performed a data-driven approach to identify all voxels where link-step propagation correlated with SOMS:CD-PHQ15 scores, and the left anterior insula was amongst the most robust areas (Supplementary Methods, Supplementary Fig. 2). Given that we previously characterized inverse correlations between left anterior insular volume and FND symptom severity,[2829] the left anterior insula (−45, 9, −9) was chosen as an additional ROI. Correction for multiple comparisons employed cluster-wise correction using Monte Carlo simulation. Post-hoc analyses evaluated if statistically significant within-group findings held adjusting for baseline: 1) mood and anxiety symptoms (BDI-II and STAI-total scores); 2) SSRI/SNRI use (yes/no); and 3) motor FND subtypes (PNES, functional movement disorders, and functional weakness).

Pilot within-group correlation with 6-month improvement

In the 22 of 30 FND subjects with prospectively collected 6-month follow-up data, a pilot analysis evaluated associations between baseline SFC and clinical outcome. The same motor and amygdalar ROIs were also used here to identify functional propagation profiles correlated with 6-month change in SOMS:CD-PHQ15 scores. The percentage change in the SOMS:CD-PHQ15 composite score was used in a single-class general linear model to study relationships between SFC and clinical outcome (scores were inverted so that higher scores reflected greater improvement). Correction for multiple comparisons applied a cluster-wise correction using a Monte Carlo simulation, and post-hoc analyses adjusted statistically significant findings for baseline: 1) BDI-II and STAI-total scores, and 2) SSRI/SNRI use. Given sample size limitations, we did not adjust for motor subtypes.

RESULTS

Motor findings

Compared to controls, the 1st link-step from left-M1 hand in patients with FND showed increased connectivity to the bilateral pre-and postcentral gyri, SMA, MCC, and superior parietal lobule (Fig. 2). In the 2nd link-step from the left-M1 hand, patients with FND also displayed enhanced propagation to the bilateral posterior insula, TPJ and putamen (in addition to the areas described in the 1st link-step which were also present). In the 3nd link-step from the left-M1 hand, patients with FND compared to controls also showed greater link-step connectivity to bilateral dorsomedial prefrontal areas. Post-hoc analyses adjusting for depression and anxiety showed enhanced propagation from the left-M1 hand to the bilateral dorsal ACC/MCC (in all 3 link-steps), dorsomedial prefrontal cortex (2nd and 3rd link-steps), and right TPJ (2nd and 3rd link-steps) in FND subjects compared to controls.

From the right-M1 hand area, patients with FND showed similar increased SFC profiles across all link-steps to those seen from the left-M1 hand compared to controls (Fig. 2). In post-hoc analyses adjusting for depression and anxiety, only increased link-step connectivity to the bilateral dorsomedial prefrontal cortex was observed in the 2nd and 3rd steps in patients with FND compared to controls.

Originating from the left-M1 foot, the 1st link-step did not show any between-group differences. In the 2nd and 3rd link-steps, patients with FND compared to controls demonstrated similar group-level differences as those described for the left and right M1 hand areas (Supplementary Fig. 3). Group-level differences did not remain significant adjusting for depression and anxiety. No other between-group differences were observed across the 6 motor ROIs.

Amygdala findings

From the right laterobasal amygdala, in the 2nd link-step patients with FND displayed enhanced propagation to the left > right anterior insula, bilateral parahippocampal and fusiform gyri, hippocampus, putamen, pallidum and the PAG compared to controls (Fig. 3). In the 3rd link-step, patients with FND showed increased connectivity to the left parahippocampal and fusiform gyri, PAG and hypothalamus. These between-group findings did not hold adjusting for depression and anxiety scores. There were no other SFC differences across the bilateral amygdala ROIs.

Exploratory interconnector analysis

When examining common M1 – right laterobasal amygdala functional propagation profiles, patients with FND compared to controls showed increased 2nd link-step connectivity to bilateral anterior insula, dorsolateral prefrontal cortex (dlPFC), putamen, left fusiform gyrus and the hypothalamus (Fig. 3). In the 3rd link-step, patients with FND compared to controls showed greater connectivity to the left anterior insula, parahippocampal and fusiform gyri, right posterior insula, bilateral putamen, PAG and hypothalamus (Fig. 3).

Within-group symptom severity analyses

There were no statistically significant relationships between motor or amygdala SFC profiles and SOMS:CD-PHQ15 scores in patients with FND.

SOMS:CD-PHQ15 scores positively correlated with enhanced left anterior insular 1st link-step connectivity to the right anterior-middle insula, MCC, inferior frontal gyrus, TPJ, bilateral precuneus, and post-central gyri in patients with FND (Fig. 4). In the 2nd link-step, FND symptom severity also positively correlated with increased left anterior insula link-step connectivity to the right anterior-middle insula, inferior frontal gyrus, premotor, SMA, TPJ, bilateral dorsal ACC/MCC, precentral/postcentral gyri, and occipital areas (Fig. 4). The 3rd link-step showed similar findings to the 2nd link-step. Of note, using Cook's distance there were no outliers.

In post-hoc analyses adjusting separately for depression/anxiety and SSRI/SNRI medication use, correlations between SOMS:CD-PHQ15 scores and left anterior insular enhanced 2nd link-step connectivity to the right anterior insula, TPJ, bilateral pre/post central gyri, and SMA remained statistically significant. Increased 2nd and 3rd link-step propagation to the dorsal ACC/MCC held adjusting for SSRI/SNRI medication use, but not for depression/anxiety. In post-hoc analyses accounting for motor FND-subtypes, FND symptom severity positively correlated with enhanced left anterior insula to right TPJ link-step connectivity across all subgroups; positive correlations between increased left to right anterior insular link-step connectivity and SOMS:CD-PHQ15 scores were most appreciable in those with functional weakness (Supplementary Fig. 4).

Within-group naturalistic 6-month outcome pilot

6-month improvement in SOMS:CD-PHQ15 scores positively correlated with left centromedial amygdalar 1st link-step connectivity to the right anterior insula, dorsal ACC/MCC, putamen and TPJ (Fig. 5). Baseline left centromedial amygdalar 2nd link-step connectivity to the right anterior insula and putamen also predicted 6-month improvement in SOMS:CD-PHQ15 scores. No outliers were identified in this 22-subject cohort using Cook's distance. A post-hoc stratified analysis (7 most improved, 7 least improved, 8 with medium-range outcomes), showed that the relationship between baseline left centromedial amygdala – right anterior insula 1st link-step stepwise functional connectivity and clinical improvement was driven by increased centromedial amygdala-anterior insula connectivity in the 7 most improved individuals compared to the other subgroups. In analyses adjusting separately for baseline depression/anxiety and antidepressant use, only associations between 1st link-step left centromedial amygdala – right anterior insula connectivity and 6-month improvement remained statistically significant.

Across the right M1-hand and left M1-foot ROIs, enhanced link-step connectivity to the left inferior temporal gyrus positively correlated with 6-month improvement in SOMS:CD-PHQ15 scores. Only the left M1-foot findings held adjusting for depression/anxiety and antidepressant use (See Supplementary Fig. 5 and Supplementary Fig. 6). No other ROIs showed any statistically significant findings.

DISCUSSION

Consistent with hypotheses, patients with FND compared to controls showed enhanced functional propagation from primary motor areas and amygdalar sub-nuclei to the multimodal integration network. Specifically, patients with FND exhibited increased link-step connectivity between motor regions and the bilateral posterior insula, MCC, TPJ, and putamen. Increased linked-step connectivity from the primary motor cortex to the bilateral MCC and right TPJ remained significant adjusting for group-level depression and anxiety scores. Beginning from the right laterobasal amygdala, the FND cohort also showed enhanced connectivity to the left anterior insula, bilateral parahippocampal/fusiform gyri, hippocampus, basal ganglia, PAG and hypothalamus; these findings, however, did not hold adjusting for depression and anxiety scores. An exploratory interconnector analysis demonstrated that link-steps to the bilateral anterior insula, dlPFC, putamen, PAG, and hypothalamus were altered across motor and amygdalar pathways in FND patients. In within-group analyses, patient-reported symptom severity positively correlated with enhanced link-step connectivity from the left anterior insula to the right anterior insula, TPJ, pre-and post-central gyri, and SMA. In a pilot analysis, increased baseline link-step connectivity from the left centromedial amygdala to the right anterior insula correlated with a more favorable 6-month prognosis. Both symptom severity and outcome related within-group findings held adjusting for depression/anxiety and antidepressant use. Collectively, these findings support aberrant delivery of motor and limbic information to higher-order multimodal integration areas in FND.

Patients with FND have been reported to exhibit an attentional bias for functional motor symptoms,[42][43] loss of sensory attenuation,[44] and impaired interoceptive accuracy.[45] In addition, some individuals with paroxysmal functional symptoms demonstrate heightened somatic and autonomic arousal without the subjective experience of anxiety (“panic without panic”).[46] Given the enhanced link-step connectivity from primary motor cortex to posterior insula and MCC observed in this study, along with heightened laterobasal amygdala to bilateral anterior insula SFC, these findings support that impaired interoceptive processing (posterior insula) and altered emotional and self-awareness (anterior insula) may be implicated in the pathophysiology of FND.[47] Regarding loss of sensory attenuation previously identified in FND,[44] it is possible that enhanced primary motor cortex to posterior insula stepwise connectivity observed in our cohort relates to this phenomenon and warrants further inquiry. Furthermore, the insula and MCC are convergent zones for negative emotional processing, nociception and cognitive control,[48] which may shed light on the neural mechanisms driving the multiplicity of sensorimotor, viscerosomatic, affective, and cognitive symptoms frequently endorsed by FND populations. Our findings also suggest that enhanced functional propagation from primary motor cortex to posterior insula, and laterobasal amygdala to anterior insula, may be at the intersection of FND symptoms and negative affect, given that these relationships did not remain significant adjusting for depression and anxiety. Interoceptive awareness tasks, particularly at the intersection of interoception and emotion processing, are needed to clarify the observations of this study.

The finding of enhanced link-step connectivity from the right laterobasal amygdala to the PAG and hypothalamus in patients with FND delineates a potential candidate mechanistic

pathway. The laterobasal amygdala receives thalamic sensory afferents, and through interneurons, connects to the centromedial nucleus of the amygdala (the output center projecting to the PAG and hypothalamus).[49] In healthy subjects, SFC propagation from the laterobasal amygdala showed strong inter-amygdalar connectivity at the first link-step (Fig. 1). By the 2nd link-step in healthy controls, the laterobasal amygdala connected to the perigenual and dorsal ACC; particularly appreciable in the 3rd link-step was downstream propagation to the PAG and hypothalamus. Given that physical events can precipitate functional neurological symptoms,[50] and that some individuals with FND endorse sensory triggers, enhanced laterobasal (sensory) amygdalar link-step functional connectivity in patients with FND suggests a pathway for early sensory-amygdalar influence over the PAG. Notably, the PAG is implicated in pain modulation, homeostasis, autonomic responses, and defensive behaviors (including tonic immobility and freezing).[51] PAG hyperactivity has also been identified in patients with FND engaged in emotion processing.[5] Increased laterobasal amygdala-PAG connectivity may also relate to sympathetic-parasympathetic imbalances characterized in FND cohorts,[52] and enhanced amygdalar–hypothalamic connectivity is consistent with reported links between threat vigilance and salivary cortisol levels in patients with FND.[53]

Primary motor areas exhibiting enhanced link-step connectivity to the posterior insula, SMA, and putamen is consistent with published reports of heightened connectivity between motor execution and limbic-paralimbic areas in FND populations.[7811–1318] The exploratory interconnector analysis suggests that the bilateral anterior insula, dlPFC, putamen, PAG, and hypothalamus may be common points of altered functional propagation across motor and amygdalar pathways. The dlPFC is implicated in executive control and top-down emotion regulation. Given that dlPFC-related functional alterations have been characterized in several FND studies,[81854] non-invasive dlPFC modulation to modify motor-limbic activity trans-synaptically may be a therapeutic intervention warranting study.

In within-group analyses adjusting for depression/anxiety and antidepressant use, a positive correlation was observed between FND symptom severity and enhanced link-step connectivity from the left anterior insula to the right anterior insula, TPJ, SMA and sensorimotor areas. We have previously characterized reduced left anterior insular volume in patients with FND associated with symptom severity.[2829] Our functional propagation findings suggest that while the left anterior insula may be an important node in the pathophysiology of FND, a network perspective incorporating the impact of abnormal integration of information from the left anterior insula to the right anterior insula, TPJ and motor regions sheds additional light on brain-symptom severity relationships. In addition, tasked-based[655] and resting-state neuroimaging abnormalities[23–25] in the TPJ/inferior parietal lobule have been characterized in FND cohorts, and linked to impaired motor attention awareness and self-agency. Enhanced insular-TPJ link-step connectivity correlating with symptom severity in our study, and previously described task-based[55] and functional connectivity alterations[25] across insular and TPJ areas, suggest that these epicenters both play important roles in promoting altered awareness in individuals with FND.

To date, no published studies have identified functional MRI biomarkers of prognosis in patients with FND. In a pilot analysis, individual differences in link-step connectivity from

the left centromedial (output) amygdala to the right anterior insula predicted 6-month improvement. Given that appreciating links between mood, psychosocial stressors and FND symptoms are core components of psychotherapy for FND,[37] we speculate that relative increases in baseline connectivity between the centromedial (output) amygdala and anterior insula may be a marker of preserved emotional awareness that potentially aids treatment response. In addition, analyses showed a possible connection between baseline primary motor cortex-left inferior temporal gyrus link-step connectivity and outcome, which may relate to emotional-linguistic processing. Larger scale studies are needed to comprehensively elucidate biomarkers predicting clinical outcomes.

Limitations include modest sample size, psychiatric comorbidities, psychotropic medication use, phenotypic heterogeneity, and sole reliance on patient-reported symptom severity measures. Given that patients with FND commonly have psychiatric comorbidities, future studies with psychiatric controls are needed to clarify our between-group findings, particularly given that some nodes in the neurobiology of FND (e.g. insula, amygdala) may be at the intersection of affective and somatic symptoms. Studies characterizing functional propagation profiles in mood/anxiety, trauma-related disorders and other functional medical syndromes are also needed to better contextualize the findings of this study. In addition, while individuals with FND frequently exhibit mixed symptoms and/or can develop new functional symptoms over the course of their illness, the use of a transdiagnostic research approach remains debated.[3056] In this study, we showed that enhanced left anterior insula to right TPJ link-step connectivity correlated with symptom severity across motor subtypes, while links between FND symptom severity and increased left to right anterior insula connectivity was most appreciable in those with functional weakness. These findings suggest some common pathophysiologic elements across motor FNDs, as well as the potential for distinct neurobiological features. More research is needed to combine patient-report scales with objective measures, as well as combining neuroimaging and questionnaire data with behavioral, neuroendocrine, and autonomic measures. Furthermore, more research is needed to investigate the relationships between primary motor cortex functional propagation profiles and specific FND symptoms (e.g. functional hand weakness vs. functional gait). Serially collected longitudinal neuroimaging data is also needed to contextualize if the findings reported here are disease-related or representative of compensatory mechanisms; additional research is needed to identify neurocircuit nodes that are essential for symptom generation, and those alterations that more closely relate to predisposing vulnerabilities and perpetuating factors. Furthermore, in addition to an important role for the multimodal integration network, altered self-referential processing and contextual appraisal warrant additional research in patients with FND.

In conclusion, we applied network graph-theory approaches to identify enhanced propagation from primary motor cortex and laterobasal amygdala to cortical-subcortical areas implicated in salience, interoception, stress responses and self/emotional awareness. Altered link-step functional connectivity from the left anterior insula to the right anterior insula and TPJ may relate to symptom severity, while centromedial amygdala–anterior insula interactions require more study as a possible outcome biomarker. These findings suggest potential candidate neurocircuit pathways in the pathophysiology of FND.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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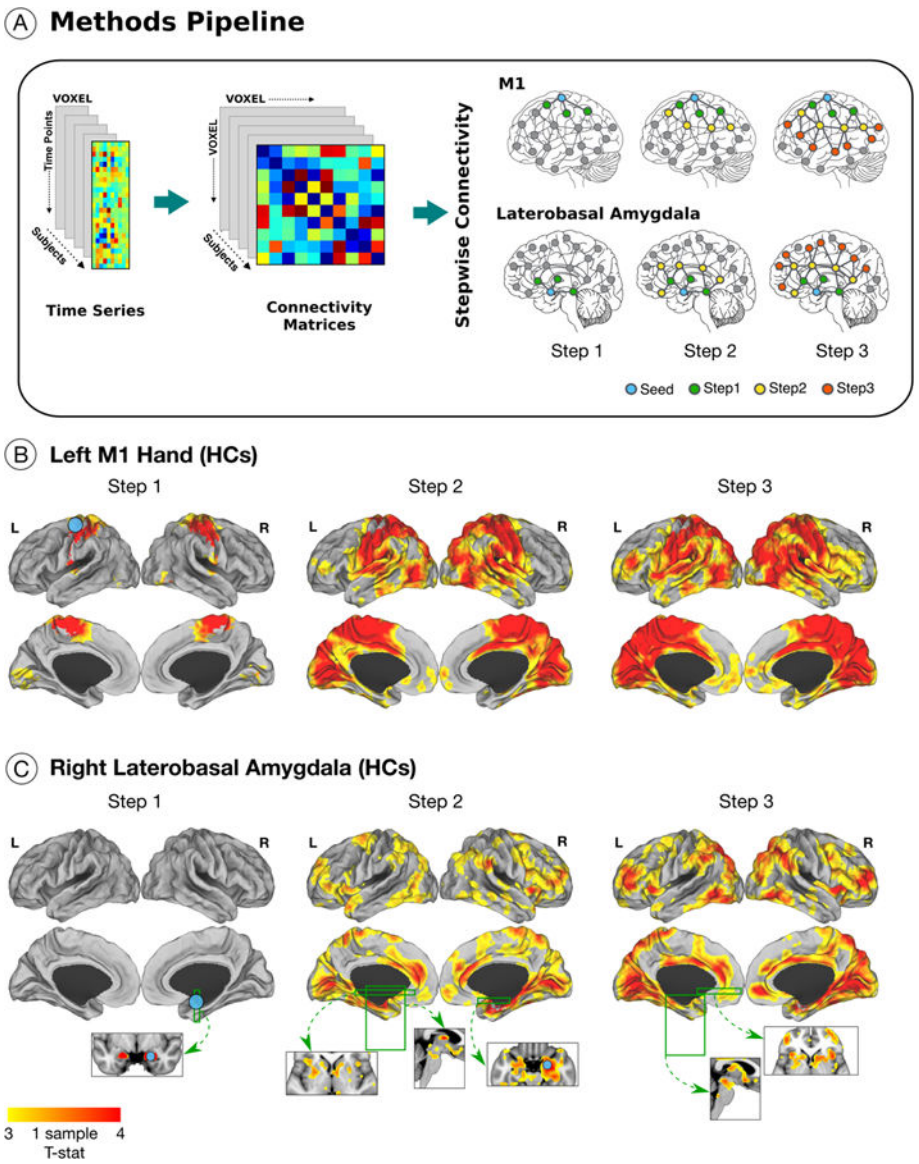

Figure 1. Stepwise functional connectivity pipeline used to characterize differences in the integration of motor and amygdalar information between patients with functional neurological disorder (FND) and healthy controls (HC).

(A) The blood-oxygen-level-dependent time series preprocessed signal was used to create a voxel by voxel connectivity matrix at the individual-subject level. Using motor and amygdalar regions-of-interest (ROIs), we computed the step-link connectivity for steps 1, 2 and 3. Green nodes represent the regions reached by the 1st link-step from the ROI (represented in blue); yellow and red nodes represent 2nd and 3rd link-steps from the ROI. As an illustrative example, panel (B) shows the functional propagation for 30 healthy subjects from the left M1-hand (one sample T-test threshold at p-value 0.01 corrected for multiple comparisons; replication of Sepulcre 2014). Panel (C) shows the functional propagation of the right laterobasal amygdala ROI in healthy subjects; one sample T-test thresholded at p-value 0.01 corrected for multiple comparisons. The 1st link-step shows connectivity to adjacent bilateral amygdalar regions. In the 2nd link-step, connectivity is

observed to cingulo-insular salience network regions among other areas; in the 3rd link-step, propagation reaches the periaqueductal gray and hypothalamus. See Supplementary Fig. 1 for delineation of link-step connectivity profiles from other amygdalar sub-nuclei in healthy subjects.

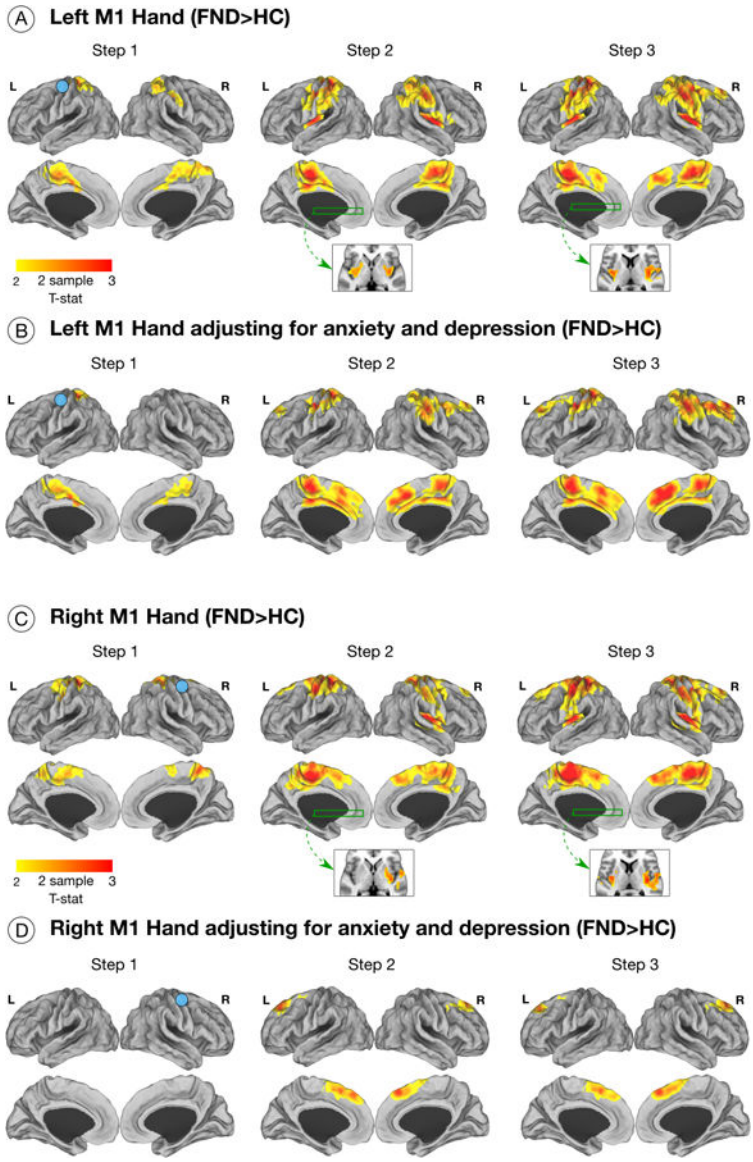

Figure 2. Altered stepwise functional propagation from primary motor areas in patients with functional neurological disorder (FND).

Maps display results of general linear models comparing functional propagation in patients with FND vs. healthy controls (HC). Only results surviving multiple comparisons are shown adjusting for age, gender and handedness. (A) Patients with FND compared to controls exhibited increased 1st link-step connectivity from the left M1-hand (right hand projected in left hemisphere) to bilateral pre-and postcentral gyri, supplementary motor area, middle cingulate cortices, and superior parietal lobule. In the 2nd link-step from the left M1-hand area, patients with FND compared to controls displayed increased connectivity to the bilateral posterior insula, temporoparietal junction (TPJ) and putamen (in addition to the areas found in the 1st-link step). In the 3rd link-step, patients with FND showed greater connectivity in bilateral dorsomedial prefrontal areas in addition to the regions observed in earlier steps. (B) Displays left M1-hand functional propagation differences between patients with FND compared to controls adjusting for depression and anxiety scores. (C-D) Depicts

results obtained from the right M1-hand in patients with FND compared to controls, which are similar to those observed for the left M1-hand region.

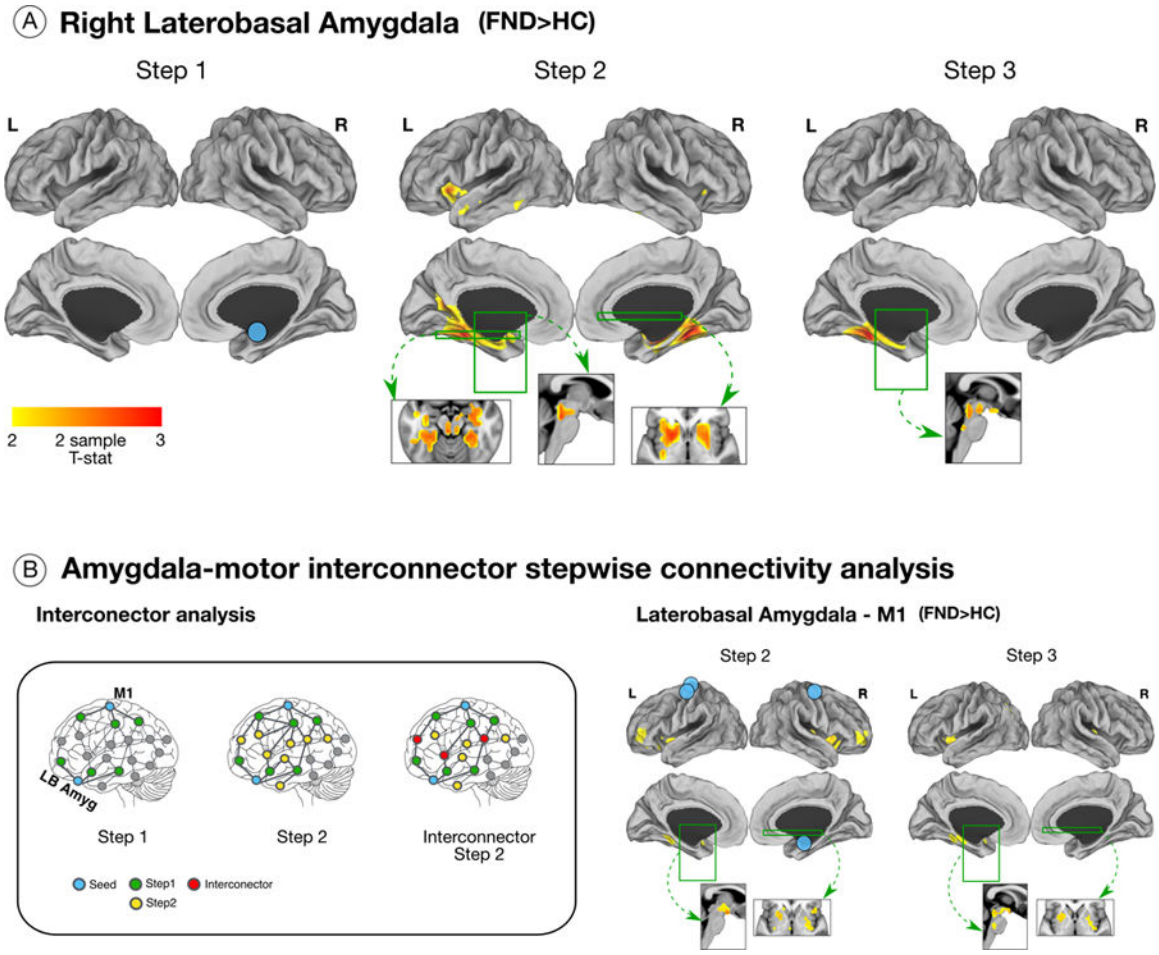

Figure 3. Altered stepwise propagation from the right laterobasal amygdala and an exploratory amygdala – motor interconnector analysis in patients with functional neurological disorder (FND).

(A) Patients with FND compared to controls showed greater 2nd link-step connectivity from the right laterobasal amygdala to the left > right anterior insula, bilateral parahippocampal and fusiform gyri, hippocampus, putamen, pallidum, and the periaqueductal gray compared to controls. Patients with FND in the 3rd link-step also showed enhanced connectivity to left parahippocampal and fusiform gyri, hypothalamus and the periaqueductal gray compared to controls. These group-level differences in right laterobasal amygdala functional propagation did not remain significant adjusting for depression and anxiety. (B) In the left panel, green nodes represent voxels within one link-step from any of the amygdala or motor regions-of-interest (ROIs, blue nodes). The next link-step from green nodes are displayed in yellow (2nd link-step). The yellow nodes present in the 2nd link-step from both amygdala or motor regions are represented in red. The nodes displayed in red represent the interconnector regions where the propagation of information between different ROIs converge. In the right panel, uncorrected right-tailed T-test results are displayed. Patients with FND compared to controls showed enhanced 2nd link-step interconnector connectivity to bilateral anterior insula, dorsolateral prefrontal cortices, putamen, left fusiform gyrus and hypothalamus. In the 3rd link-step, higher connectivity was observed in left anterior insula, parahippocampal

and fusiform gyri, right posterior insula, bilateral putamen, periaqueductal gray and hypothalamus in patients with FND compared to controls.

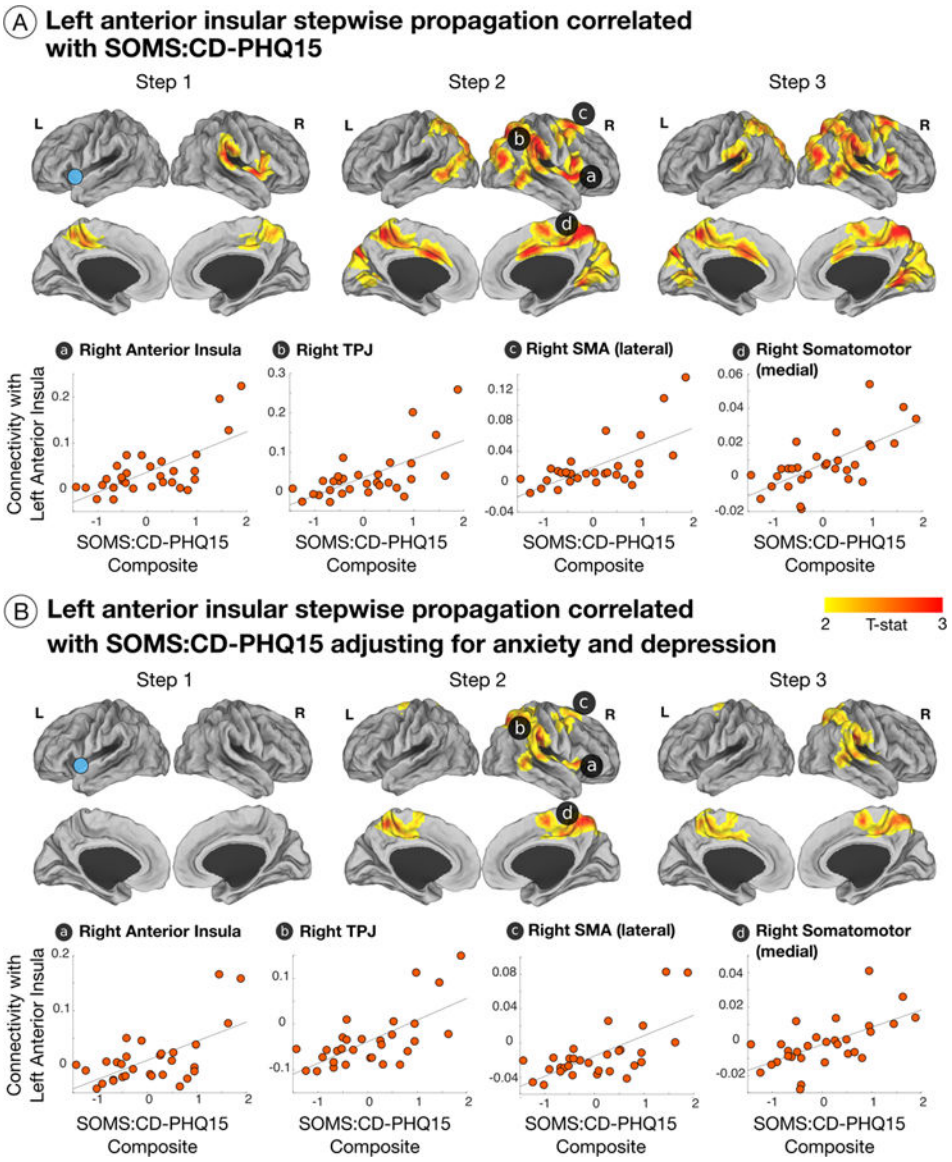

Figure 4. Insular stepwise functional connectivity correlated with symptom severity in patients with functional neurological disorder (FND).

(A) 1st link-step showed a positive correlation between patient-reported symptom severity and increased left anterior insula to right anterior insula, middle cingulate cortex, inferior frontal gyrus, temporoparietal junction (TPJ), bilateral precuneus, and postcentral gyri link-step connectivity. For the 2nd link-step, this correlation included the right anterior insula, inferior frontal gyrus, premotor, supplementary motor area (SMA), TPJ, bilateral dorsal anterior cingulate/middle cingulate cortices, precentral/postcentral gyri, and occipital areas. The 3rd link-step showed similar results to the 2nd link-step. Scatter plots display findings with a T statistic > 4 in the 2nd link-step. (B) Displays the correlations between patient-reported symptom severity and left anterior insula functional propagation profiles adjusting for anxiety and depression.

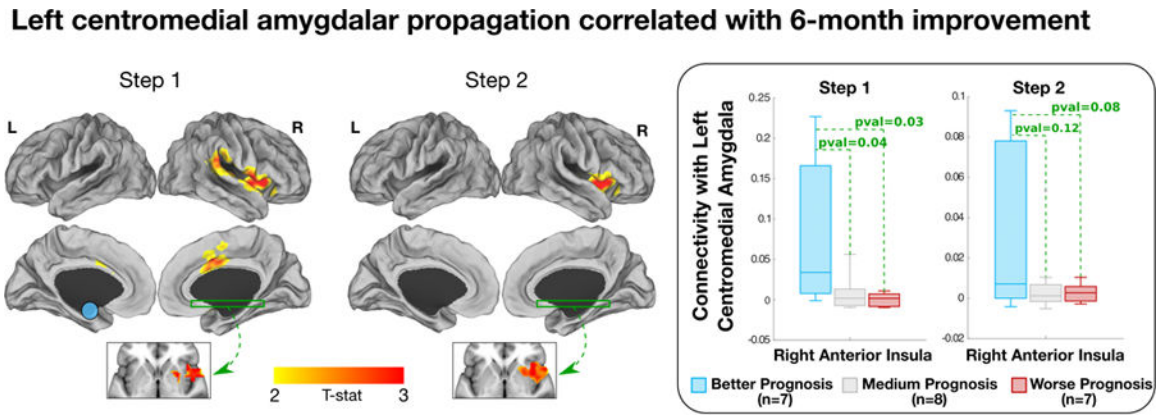

Figure 5. Pilot stepwise functional connectivity correlations with 6-month clinical improvement in patients with functional neurological disorder (FND).

The 1st link-step showed a correlation between better 6-month clinical outcomes and higher left centromedial amygdala connectivity to the right anterior insula, putamen, dorsal anterior cingulate cortex/middle cingulate cortex and TPJ. For the 2nd link-step, improvement positively correlated with left centromedial amygdala connectivity to the right anterior insula and putamen. In additional post-hoc analyses, patients with FND were stratified in three groups: better prognosis (N=7), medium prognosis (N=8) and worse prognosis (N=7). Boxplots show that the relationship between left centromedial amygdalar – right anterior insula 1st link-step stepwise functional connectivity and clinical improvement was driven by increased centromedial amygdala-anterior insula connectivity in the 7 most improved individuals compared to the other sub-groups.