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Chapter 14

The role of the anterior and midcingulate cortex in the neurobiology of functional neurologic disorder

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Abstract

Functional neurologic disorder (FND)/conversion disorder is a prevalent and disabling condition at the intersection of neurology and psychiatry. Clinicians often report feeling ill-equipped treating patients with FND, perpetuated by a historically limited understanding of neurobiologic disease mechanisms. In this review, we summarize the neuroimaging literature across the spectrum of sensorimotor FND, including functional imaging studies during rest, sensorimotor performance, and emotional-processing tasks as well as structural magnetic resonance imaging findings. Particular attention is given to studies implicating the anterior and middle cingulate cortex and related salience network structures (insula, amygdala, and periaqueductal gray) in the neurobiology of FND. Neuroimaging studies identify cingulo-insular functional alterations during rest, motor performance, and emotion processing in FND populations. The literature also supports that patients with FND exhibit heightened amygdalar and periaqueductal gray reactivity to emotionally valenced stimuli, enhanced coupling between amygdalar and motor control areas, and increased amygdalar volumes. The structural neuroimaging literature also implicates cingulo-insular areas in the pathophysiology of FND, though these findings require replication and clarification. While more research is needed to fully elucidate the pathophysiology of FND, salience network alterations appear present in some FND populations and can be contextualized using biopsychosocial models for FND.

INTRODUCTION

Functional neurologic disorder (FND) is a common neuropsychiatric condition defined by neurologic symptoms that are incompatible with other medical-neurologic conditions and that encompasses functional weakness (FW), functional movement disorders (FMD), psychogenic nonepileptic seizures (PNES, also known as dissociative seizures), functional speech, and/or nondermatomal sensory deficits (functional numbness) among other symptoms (Espay et al., 2018a). With the *Diagnostic and Statistical Manual of Mental Disorders*—5th edn, FND was redefined as a "rule-in" condition based on neurologic exam signs, removing the need to identify a proximal stressor (Stone et al., 2010b, 2011). Importantly, FND is the second-most common referral to outpatient neurology (Stone et al., 2010a), and somatic symptom disorders more broadly account for approximately 256 billion dollars a year in healthcare expenses (Barsky et al., 2005). FND is also an important cause of disability and reduced health-related quality of life (Jones et al., 2016). Despite the frequency with which

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clinicians encounter this population, both neurologists and psychiatrists report feeling ill-equipped caring for patients with FND and lack an updated conceptual model for this condition (Kanaan et al., 2009; Perez et al., 2012).

Clinical and neurobiologic formulations of FND are rooted in the biopsychosocial model, with important roles for predisposing, precipitating, and perpetuating factors (McKee et al., 2018; Pick et al., 2018). Adverse life events are a commonly recognized predisposing vulnerability for FND linked to symptom severity (Roelofs et al., 2002; Selkirk et al., 2008; Perez et al., 2017a; Keynejad et al., 2018), although not all individuals with FND endorse prior traumatic experiences. A recent metaanalysis found that a history of maltreatment and stressful life events is common in patients with FND, highlighting important roles for emotional neglect along with physical and sexual abuse (Ludwig et al., 2018).

While a limited understanding on the pathophysiology of FND has impeded the development of novel therapies and biomarkers, in vivo neuroimaging research and renewed clinical interest have catalyzed efforts to elucidate the neurobiology of this enigmatic condition. Although the emerging neurobiology of FND suggests that this condition reflects a multinetwork problem (Aybek and Vuilleumier, 2016; Szaflarski and LaFrance Jr, 2018), structural and functional neuroimaging studies highlight important links between FND and alterations in the anterior cingulate cortex (ACC), midcingulate cortex (MCC), and related salience network areas (Seeley et al., 2007).

The salience network is implicated in multimodal integration, negative emotion processing, cognitive control, nociception, interoception, and arousal, among other neurobiologic processes (Seeley et al., 2007). In this narrative review, as part of a volume dedicated to the cingulate gyrus, we outline the neuroimaging literature implicating the ACC, MCC, and related salience network areas (amygdala, insula, periaqueductal gray (PAG)) in the pathophysiology of FND. Our anatomic nomenclature for parcellating the cingulate cortex is specified in Chapter 1 of this volume (Vogt, 2019). We focus on studies comparing FND to healthy controls as well as within-group designs, excluding comparisons to feigning or neurologic controls, which are beyond the scope of this chapter (Spence et al., 2000; Stone et al., 2007; Cojan et al., 2009). Thereafter, we contextualize functional and structural salience network alterations in FND as linked, in part, to disturbances in multimodal integration, self/emotional awareness, emotion processing, interoception, and defensive behaviors (Pick et al., 2018).

REVIEW

Task-based neuroimaging

Motor tasks

One of the first FND neuroimaging studies was performed in 1997 by Marshall and colleagues on a 45-year-old woman with functional left hemiparesis using positron emission tomography (PET) during performance of bilateral motor preparation and movement tasks (Marshall et al., 1997). Attempting to move the affected vs unaffected leg revealed right ACC and orbitofrontal cortex hypermetabolism. This early finding was interpreted as potential evidence for paralimbic mediated inhibition of motor cortices.

Several subsequent studies used task functional magnetic resonance imaging (fMRI) motor paradigms to investigate the pathophysiology of FND (de Lange et al., 2007; Stone et al., 2007; Voon et al., 2010b, 2011; Czarnecki et al., 2011; Van Beilen et al., 2011; Saj et al., 2014). Voon, Hallett, and colleagues examined eight patients with a positional functional tremor, instructing individuals to either hold their limb in a position that triggered symptoms or to voluntarily mimic the tremor in the same arm (Voon et al., 2010b). Functional tremor, compared to volitional movements, showed decreased right temporoparietal junction (TPJ) activity; a complementary seed-based connectivity analysis displayed decreased coupling between the right TPJ and bilateral sensorimotor cortices, subgenual ACC (sACC), cerebellar vermis, right precuneus, and left ventral striatum. Importantly, the TPJ is implicated in sense of agency and motor intention awareness (Desmurget et al., 2009). Furthermore, a recent task fMRI study examined sense of agency in 21 patients with FMD compared to 20 healthy controls (HCs) as individuals moved their right hand and watched a projection of a hand that responded to a variable percentage of their movements (Nahab et al., 2017). Interestingly, patients with FMD reported feeling in greater control when they had none and underreported feeling in control when they in fact were. The hemodynamic responses of the right anterior insula and TPJ in patients with FMD, compared to healthy subjects, showed a reduced ability to differentiate the degree of subject control in task performance.

Other studies in FMD have further characterized neural circuit activations during motor tasks. A single-photon emission computed tomography (SPECT) study in patients with functional tremor compared to controls probed regional cerebral blood flow (rCBF) during a repetitive motor task (taking a cup from a table to the face) (Czarnecki et al., 2011). Patients with functional tremor in the task vs rest neuroimaging contrast revealed

perigenual ACC (pACC) and ventromedial prefrontal hypoperfusion, along with increased cerebellar rCBF. In addition, patients with functional tremor exhibited increased left insular rCBF at rest compared to controls. A PET study compared six patients with functional dystonia to six HCs during rest, fixed right leg posturing, and paced ankle movements (Schrag et al., 2013). Averaging across all tasks, patients with functional dystonia, compared to controls, showed decreased left posterior MCC (pMCC), supplementary motor area (SMA), motor cortex, TPJ, inferior parietal lobule, and right inferior frontal cortex metabolism, as well as increased right TPJ and basal ganglia metabolism. An fMRI study in 11 individuals with FMD, compared to HCs, probing internally vs externally generated movements (Voon et al., 2011) reported that patients showed increased right amygdala, left anterior insula, and bilateral posterior cingulate cortex activations, along with decreased left SMA activity, during internally generated movements. Collectively, these findings identify altered cingulo-insular and amygdalar activations during motor behaviors (Czarnecki et al., 2011; Voon et al., 2011; Schrag et al., 2013) and at rest (Czarnecki et al., 2011) in FND cohorts.

In FW populations, motor fMRI paradigms have also been used. A study by Stone and colleagues in four patients with functional leg weakness probed activations during leg movements (Stone et al., 2007). During attempted movements of the weak vs nonaffected limb, patients displayed increased basal ganglia, lingual gyri, and inferior frontal cortex activations, along with decreased right prefrontal cortex activations; exploratory, uncorrected analyses also revealed increased bilateral insula activity. Another study in eight patients with FW used a mental hand rotation paradigm to characterize impaired motor conceptualizations (de Lange et al., 2007). When presented with affected vs unaffected hand images, patients showed increased left ventromedial (extending to the pACC) and dorsomedial prefrontal activity. Another study of two patients with FW found bilateral insular activation during attempted movement and during mental rotation of the affected vs unaffected limb (Saj et al., 2014). Additionally, one of the patients exhibited ACC hyperactivation during image rotation of the affected vs unaffected extremity. Finally, a study comparing patients with FW to controls identified that during movements of their affected limb, patients showed increased premotor, pMCC, and supramarginal gyrus activity, as well as decreased prefrontal and precuneus activity (Van Beilen et al., 2011). Interestingly, MCC hyperactivations were partially independent of FW lateralization.

One study evaluated metacognitive abilities in 10 patients with mixed sensorimotor FND vs HCs attempting to draw straight lines toward a target, with the trajectory systematically deviating and patients rating their appreciation of any deviations (Bègue et al., 2018). When deviations were detected vs undetected, patients, compared to controls, displayed increased right superior frontal gyrus activity and decreased anterior MCC (aMCC), pre-SMA, middle occipital gyrus, and right inferior temporal gyrus activity. When judging confidence in their control of movements, patients, compared to controls, exhibited increased bilateral hippocampal/parahippocampal and left amygdala activity.

To summarize, studies across the spectrum of FND using motor-related fMRI tasks revealed functional alterations in key nodes of the salience network (ACC, MCC, insula, amygdala) (Marshall et al., 1997; de Lange et al., 2007; Czarnecki et al., 2011; Van Beilen et al., 2011; Voon et al., 2011; Saj et al., 2014; Nahab et al., 2017; Bègue et al., 2018) as well as areas involved in self-agency perception (right TPJ) (Voon et al., 2010b; Schrag et al., 2013; Nahab et al., 2017), during performance of motor behaviors. Several studies have characterized cingulo-insular (including pACC and MCC) hyperactivations during motor tasks (Marshall et al., 1997; de Lange et al., 2007; Saj et al., 2009; Van Beilen et al., 2011; Voon et al., 2011), although the directionality of these findings has not been consistent across all studies (Czarnecki et al., 2011; Schrag et al., 2013).

Sensory processing tasks

fMRI studies applying tactile stimuli to individuals with nondermatomal sensory deficits also highlight a role for the ACC and MCC in the pathophysiology of functional numbness (Mailis-Gagnon et al., 2003; Saj et al., 2009; Burke et al., 2014). One report examined four patients with functional sensory loss using either painful or innocuous stimuli applied to either the affected or unaffected extremity (Mailis-Gagnon et al., 2003). Unperceived vs perceived stimuli failed to activate the primary somatosensory cortex, anterior insula, aMCC, and thalamus among other areas. A larger study of 10 individuals with functional numbness showed that vibrotactile stimulation applied to the numb vs unaffected limb resulted in greater bilateral dorsolateral prefrontal cortex (dlPFC), right pACC, insula, TPJ, orbitofrontal cortex (OFC), and striatal-thalamic activations (Burke et al., 2014). Finally, a case report of a 56-year-old female presenting with left arm and leg FW, functional numbness, and spatial neglect showed bilateral aMCC hyperactivations during line bisection performance (Saj et al., 2009). Together, these findings point toward ACC/MCC alterations in individuals experiencing functional somatosensory deficits; however, more research is needed to determine subregion specificity and directionality of findings.

Emotion-processing tasks

Several studies have used emotionally valenced probes to investigate emotion processing in patients with FND, identifying increased amygdalar and related salience network activity (Kanaan et al., 2007; Voon et al., 2010a; Aybek et al., 2014, 2015; Hassa et al., 2017; Pick et al., 2018; Espay et al., 2018b, c). In an early case, a 37-year-old woman with a history of early life abuse and presenting with PNES and FW was scanned while listening to distressing autobiographic probes. Repressed memories vs other recollections elicited greater right amygdalar, cingulate gyrus, inferior frontal, and parietal activity, as well as decreased left primary motor cortex activity (Kanaan et al., 2007). In a related study by Aybek and colleagues in 12 individuals with FW compared to HCs, events with high escape potential vs other cues resulted in increased right sensory motor cortex, SMA, superior temporal, insular, angular gyrus, and TPJ activations (Aybek et al., 2014). Processing of distressing stimuli without escape potential in patients with FW showed decreased left hippocampal/parahippocampal activity. A seed-based functional connectivity analysis from the SMA in this cohort revealed increased coupling with the amygdala and subcortical structures. These findings provide early evidence of heightened amygdalar activity and increased coupling with motor control areas during the processing of affectively laden memories.

Studies in FND populations have also investigated emotion processing using face-viewing tasks. Increased task-based amygdalar reactivity and amygdala–SMA functional connectivity was characterized by Voon and colleagues in 16 patients with FMD compared to controls (Voon et al., 2010a). This study identified impaired habituation of amygdalar responses to emotionally valenced stimuli. Another study employing emotionally valenced faces used a hypothesis-driven approach to identify sustained (sensitized) amygdalar activation to fearful stimuli in patients with FW compared to controls (Aybek et al., 2015). At the whole-brain level, increased bilateral SMA, left dlPFC, aMCC, and PAG activity were also identified (see Fig. 14.1). A more recent study probed motor-emotion processing in 13 patients with FW compared to HCs using a dual passive movement and implicit emotionally valenced facial-viewing task (Hassa et al., 2017). During passive movements of the affected vs unaffected limb X exposure to sad vs calm faces, patients, compared to controls, displayed increased left amygdalar activity. Similar to earlier studies (Voon et al., 2010a; Aybek et al., 2014), left amygdalar seed-based functional connectivity analyses revealed increased coupling to the SMA (including pre-SMA) and the subthalamic nucleus.

Espay and colleagues examined 27 patients with functional tremor compared to HCs using (1) a finger-tapping task and (2) an implicit emotionally valenced facial task displaying either basic or intense emotions (Espay et al., 2018c). During finger tapping, patients, compared to controls, showed reduced left precentral gyrus activation, which did not remain significant controlling for depression. During the basic emotion task, patients with functional tremor displayed increased bilateral ACC and left Heschl's gyrus activity. A left amygdala seed-based functional connectivity analysis during intense emotion processing revealed enhanced left amygdala–dorsomedial prefrontal cortex coupling that remained significant, controlling for depression in patients with FMD. Another study by Espay and colleagues used the same set of paradigms to characterize 12 patients with functional dystonia compared to 25 HCs (Espay et al., 2018b). During the basic emotion task, patients, compared to controls, exhibited decreased bilateral precuneus, fusiform gyrus, cerebellum, and right middle temporal gyri activity. During the intense emotion task, patients showed decreased left insular and motor cortex activations, along with increased left occipital cortex and fusiform gyrus activations.

Across face emotion processing studies in patients with FND, commonly identified alterations included increased amygdalar reactivity and enhanced connectivity between the amygdala and motor planning/control areas (including the SMA) (Kanaan et al., 2007; Voon et al., 2010a; Aybek et al., 2014, 2015; Hassa et al., 2017). Additionally, alterations in other key nodes of the salience network including the ACC, aMCC, PAG, and the insula have been reported during emotion processing in some studies (Aybek et al., 2014, 2015; Espay et al., 2018b, c).

Resting-state functional connectivity findings in FND

Resting-state functional connectivity (rs-FC) techniques have also been applied to investigate network alterations in FND. rs-FC MRI can use region-of-interest (ROI) seed-based techniques that examine correlations between the time series of a target region and its relationship to whole-brain connectivity profiles. Other data-driven computational methods not restricted to target region-of-interest analyses include independent component analyses or graph theory approaches. Across these techniques, several studies have identified aberrant salience network functional connectivity (van der Kruijs et al., 2012, 2014; Ding et al., 2013; Arthuis et al., 2015; Li et al., 2015a, b; Morris et al., 2017; Szaflarski et al., 2018), as well as more widely distributed alterations within sensorimotor, executive control, and default mode networks (Ding et al., 2014; Maurer et al., 2016a).

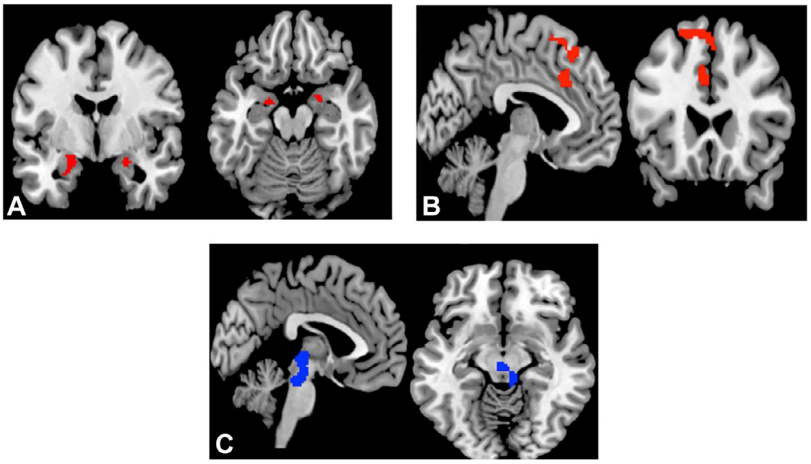

Fig. 14.1. Hyperactivation of the amygdala (panel A), anterior midcingulate cortex (panel B), and periaqueductal gray (panel C) in patients with motor functional neurologic disorder compared to controls during emotionally valenced face processing. Images provided courtesy of Selma Aybek and Timothy Nicholson and are based on the Aybek, S., Nicholson, T.R., O'Daly, O., et al., 2015. Emotion–motion interactions in conversion disorder: an FMRI study. PLoS One 10, e0123273 publication.

Hypothesis-driven seed-based analyses

Two studies used task-based activation profiles to determine seed ROIs for rs-FC analyses in FND populations (van der Kruijs et al., 2012; Szaflarski et al., 2018). The first compared 11 patients with PNES to 12 HCs by obtaining rs-FC MRI seed regions from the activation maps of picture-encoding and Stroop color-naming fMRI tasks (van der Kruijs et al., 2012). Although there were no group-level task activation differences, patients with PNES, compared to controls, displayed increased rs-FC between emotion processing (pACC, insula), motor control (precentral sulcus, central sulcus), and executive/attentional control (inferior frontal gyrus, parietal cortex) areas. Specifically, increased coupling was observed between the right pACC, insula, and left precentral sulcus. Additionally, increased ACC–inferior frontal gyrus coupling in individuals with PNES correlated with dissociation severity. The second study used task and rs-FC to compare 12 patients with PNES to 24 HCs (Szaflarski et al., 2018). An implicit emotionally valenced face-viewing task identified 10 brain areas showing differential activations in patients with PNES, which were then chosen as ROIs in addition to the amygdala. During emotion processing, patients with PNES, compared to HCs, showed increased visual, temporal, and/or parietal activations and decreased cingulo-insular, inferior frontal, parahippocampal, putamen, and cerebellar activations. In rs-FC analyses, patients with PNES, compared to controls, exhibited increased left parahippocampal gyrus/uncus–right temporal connectivity. In amygdalar seed-based analyses, there were no statistically significant rs-FC differences between individuals with PNES and HCs.

Several studies have also characterized rs-FC profiles using a priori seeds. One study assessed insular subregion (anterior, mid, and posterior) connectivity in 18 patients with PNES compared to 20 HCs (Li et al., 2015b). In patients, compared to controls, the right dorsal anterior and posterior insula showed increased coupling with the left superior parietal gyrus and putamen. Furthermore, the left ventral anterior insula showed increased connectivity with the bilateral SMA, left postcentral gyrus, and right lingual gyrus. Left ventral anterior insula to bilateral SMA rs-FC correlated positively with seizure frequency. Another study also showed that ACC-SMA connectivity strength correlated positively with PNES frequency (Li et al., 2015a), providing emerging evidence that enhanced coupling between cingulo-insular areas and the SMA relate to nonepileptic seizure frequency.

The effects of negative conditioning on avoidance learning and amygdala resting-state profiles were investigated in 25 FND patients vs 20 HCs (Morris et al., 2017). To assess the effects of negative conditioning on goal-directed avoidance learning, subjects were conditioned to aversive and neutral stimuli. Then during scanning, subjects performed an instrumental associative learning task to avoid monetary losses in the context of the previously conditioned stimuli. Patients with FND, compared to controls, revealed increased bilateral amygdala and reduced left dlPFC activations when receiving negative feedback; rs-FC analyses demonstrated increased bilateral amygdala-to-right dlPFC coupling.

A recently published rs-FC in 30 patients with motor FND vs 30 controls used a graph theory stepwise functional connectivity approach to examine the flow of information from primary motor areas and amygdalar

nuclei (laterobasal, centromedial) to the rest of the brain (Diez et al., 2019). Adjusting for depression and anxiety, compared to controls, patients with FND exhibited increased link-step connectivity from primary motor cortex to bilateral MCC and right TPJ; patients with FND also showed enhanced motor cortex to posterior insula information flow that did not remain significant adjusting for depression and anxiety. Compared to controls, patients with FND showed increased link-step functional connectivity from the right laterobasal amygdala to the left anterior insula, PAG, and hypothalamus (results did not hold adjusting for depression/anxiety). Information flow from the left anterior insula to the right anterior insula, TPJ, precentral gyrus, and SMA correlated positively with patient-reported symptom severity adjusting for individual differences in depression and anxiety scores.

As a follow-up to earlier work by Voon et al. (2011), neural mechanisms underlying impaired self-agency were investigated in 35 patients with FMD compared to matched HCs (Maurer et al., 2016a). Patients with FMD exhibited decreased right TPJ coupling to bilateral sensorimotor cortex, SMA, and right insula. Patients vs HCs also exhibited a correlation between right TPJ–left insula connectivity strength and childhood emotional abuse burden. These findings support aberrant feedforward processing (sensorimotor–right TPJ connectivity) and right TPJ–left insular connectivity as implicated in impaired awareness in patients with FMD.

Data-driven analyses

One study used independent component analyses to compare 21 patients with PNES to 27 HCs (van der Kruijs et al., 2014). Five components (networks) were selected: frontoparietal, executive control, sensorimotor, default mode, and visual networks. Patients with PNES, compared to controls, showed (1) increased orbitofrontal, insular, and sACC contributions to the frontoparietal network; (2) enhanced cingulo-insular connectivity to the executive control network; and (3) increased cingulate gyrus, superior parietal lobe, pre- and postcentral gyri, and SMA coactivations to the sensorimotor network. Notably, the connectivity strengths within these networks correlated with dissociation severity.

Ding and colleagues conducted two rs-FC studies in the same PNES cohort (Ding et al., 2013, 2014). The first investigated structural and functional connectivity using rs-FC and diffusion tensor weighted imaging (Ding et al., 2013). Patients with PNES, compared to HCs, demonstrated reduced strength of both structural and functional connections in attentional, sensorimotor, and default mode networks. Moreover, in weighted structural connectivity analyses, patients with PNES showed altered nodal characteristics including (1) decreased connectivity strength, efficiency, and betweenness in bilateral insula and (2) increased betweenness in bilateral amygdala. The coupling strength of structural-functional connectivity was decreased in patients with PNES, and this finding differentiated individuals with PNES from HCs with 75% sensitivity and 77% specificity. A second study used functional connectivity density mapping to assess long- and short-range connections, showing that patients with PNES, compared to controls, revealed differences in long- and short-range connectivity in bilateral cingulo-insular, frontal, sensorimotor, and occipital brain regions (Ding et al., 2014). In another study using a whole-brain network approach in 7 patients with acute-onset, unilateral FW, compared to 15 HCs (Monsa et al., 2018), mean connectivity scores in 10 large-scale brain networks were extracted. Intranetwork analyses revealed increased rs-FC strength within the default mode network in patients with FND. Between-network analyses revealed decreased limbic/salience network–default mode network connectivity and increased limbic/salience network—temporo-parieto-occipital junction connectivity in patients. These results highlight that cingulo-insular areas display aberrant connectivity with brain areas outside the boundaries of the salience network, including abnormal interactions with the default mode network.

Wegrzyk and colleagues used graph theory to compare rs-FC profiles in 23 FND patients to 25 HCs (Wegrzyk et al., 2018). This study classified whole-brain data using machine classification. The accuracy, specificity, and sensitivity were more than 68% in differentiating patients with motor FND from HCs. The differentiating profiles in those with FND vs HCs included (1) heightened right caudate connectivity to the left amygdala and bilateral postcentral gyri; (2) enhanced paracentral lobule–prefrontal connectivity; and (3) decreased right temporoparietal (including the inferior parietal lobule)–prefrontal connectivity.

In a PET rs-FC study conducted in 16 patients with PNES compared to 16 HCs, bilateral ACC/aMCC and right inferior parietal hypometabolism were observed in patients with PNES (see Fig. 14.2) (Arthuis et al., 2015). In connectivity analyses, individuals with PNES, compared to controls, showed increased coupling between the bilateral ACC/aMCC and the left parahippocampal gyrus as well as increased right inferior parietal–bilateral cerebellum connectivity.

In summary, convergent rs-FC findings point toward alterations in brain networks mediating emotional processing, regulation, and awareness (ACC/aMCC, insula, amygdala), behavioral inhibition and cognitive control (aMCC inferior frontal gyrus, dlPFC), sense of agency (PCC/TPJ, precuneus), and motor behavior (SMA, cerebellum) in FND populations.

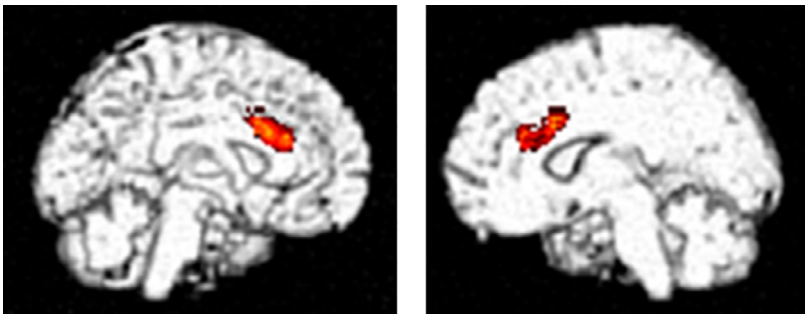

Fig. 14.2. Hypometabolism of the anterior cingulate and anterior midcingulate cortices at rest in patients with psychogenic nonepileptic seizures compared to controls. Images provided courtesy of Eric Guedj and Aileen McGonigal and are based on the Arthuis, M., Micoulaud-Franchi, J.A., Bartolomei, F., et al., 2015. Resting cortical PET metabolic changes in psychogenic non-epileptic seizures (PNES). J Neurol Neurosurg Psychiatry 86, 1106–1112 publication.

Structural MRI findings

Structural MRI studies have also characterized salience network alterations in several FND cohorts. One study compared 20 patients with PNES to 40 HCs using voxel-based morphometry (VBM) and FreeSurfer cortical thickness approaches (Labate et al., 2012). In VBM analyses, patients with PNES, compared to controls, exhibited reduced right MCC, SMA, precentral and postcentral gyri, middle frontal gyrus, and bilateral cerebellar volumes. Cortical thickness was also decreased in the right precentral, paracentral, and superior frontal gyri and the precuneus in individuals with PNES compared to controls. In within-group analyses, left inferior frontal cortical thickness correlated negatively with somatoform dissociation scores. Another cortical thickness study in 37 patients with PNES and 37 HCs (Ristić et al., 2015) identified that patients with PNES displayed increased bilateral medial OFC and left insula and lateral OFC cortical thickness, as well as cortical thinning in bilateral precentral gyrus and right entorhinal and lateral occipital areas. Finally, a recently published VBM study comparing 48 patients with FMD to 55 HCs identified increased bilateral thalamic, left amygdalar, striatal, fusiform gyrus, and cerebellar gray matter, along with reduced left sensorimotor cortex volumes (Maurer et al., 2018). Structural alterations did not correlate with indices of symptom severity or illness duration in this study.

Perez and colleagues performed two VBM studies using complementary within-group and between-group analyses to examine relationships between structural anatomy and indices of patient-reported symptom severity and adverse life event burden (Perez et al., 2017a, b). The first study examined within-group differences in 23 patients with mixed motor FND (Perez et al., 2017a). Although there were no statistically significant associations between FND symptom severity and volumetric profiles across the whole cohort, left anterior insular volumes correlated negatively with patient-reported symptom severity in the subset of 18 women with FND. Additionally, childhood abuse burden correlated negatively with left anterior insular volumes in women with FND, and adverse life event burden across the life span correlated with reduced left hippocampal volumes across all patients. Furthermore, posttraumatic stress disorder (PTSD) symptom severity related inversely to pACC volumes across the entire cohort. These observations provide early evidence that patient-reported FND and PTSD severity map onto distinct nodes of the salience network (see Fig. 14.3). In a follow-up study conducted in an expanded cohort of 26 patients with motor FND and 27 HCs, there were no statistically significant group-level volumetric findings across the whole group (Perez et al., 2017b). However, stratified between-group analyses showed that patients with FND reporting the most impaired physical health exhibited decreased left anterior insular gray matter volumes compared to controls. Furthermore, patients reporting the most severe mental health deficits displayed increased right posterior–lateral cerebellar gray matter volumes (a component of the salience network). In addition, individual differences in right amygdalar volumes correlated with elevated trait anxiety and poor mental health overall; relative increases in PAG volume correlated with role limitations due to emotional problems in patients with FND.

Using FreeSurfer surface-based analyses, the same group examined associations between somatoform and psychologic dissociation in 26 patients with motor FND compared to controls (Perez et al., 2018a). Patients with high somatoform dissociation scores (based on patient-reported symptoms over the past year), compared to controls, displayed reduced left aMCC cortical thickness. Using a within-group design, left aMCC cortical thickness correlated inversely with somatoform dissociation scores across the entire FND cohort (see Fig. 14.4). In post hoc analyses, this finding remained significant controlling for anxiety/depression, borderline personality disorder, PTSD, adverse life events, and FND subtype.

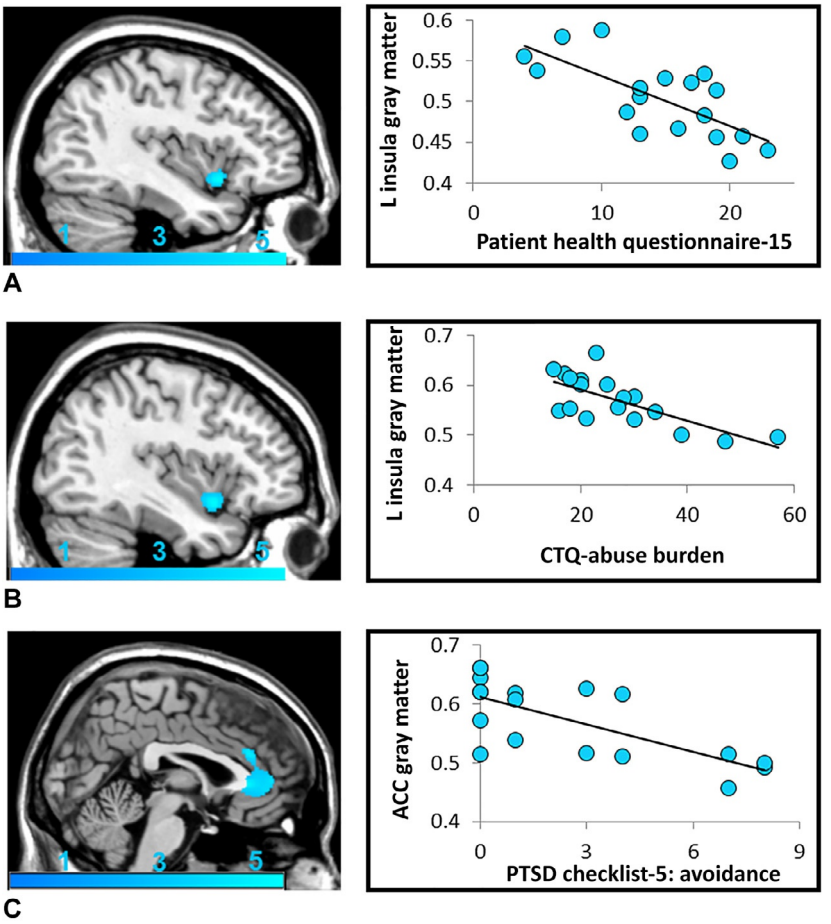

Fig. 14.3. Women with motor functional neurologic disorders showed that reduced gray matter volume in the left anterior insula correlated with the magnitude of functional somatic symptoms (panel A) and childhood abuse burden (panel B). By contrast, post-traumatic stress disorder avoidance symptoms inversely correlated with perigenual anterior cingulate cortex (pACC) gray matter volumes. Images provided courtesy of David Perez and are based on the Perez, D.L., Matin, N., Barsky, A., et al., 2017a. Cingulo-insular structural alterations associated with psychogenic symptoms, childhood abuse and PTSD in functional neurological disorders. J Neurol Neurosurg Psychiatry 88, 491–497 publication.

In summary, structural neuroimaging studies in patients with FND have begun to reveal convergent alterations in key salience network structures including reduced cingulo-insular volumes (Labate et al., 2012; Perez et al., 2017b) and relative increases in amygdalar volumes (Perez et al., 2017b; Maurer et al., 2018). Moreover, early work suggests possible important correlations between volumetric alterations in salience network structures and markers of symptom severity (Labate et al., 2012; Perez et al., 2017a, b, 2018a).

DISCUSSION

Functional and structural neuroimaging studies in patients with FND demonstrate a role for the ACC, aMCC, and related salience network structures in the pathophysiology of FND (Perez et al., 2012, 2015). Several nuclear medicine studies have reported altered perfusion or metabolism in the ACC/aMCC across the spectrum of motor FND during rest and movement (Marshall et al., 1997; Czarnecki et al., 2011; Schrag et al., 2013; Arthuis et al., 2015); rs-FC studies have also identified the ACC as a commonly altered node in patients with PNES compared to controls (van der Kruijs et al., 2012, 2014). Moreover, task fMRI studies identify altered ACC/aMCC activity during motor conceptualization (de Lange et al., 2007; Saj et al., 2014), metacognition (Bègue et al., 2018), and emotion processing (Kanaan et al., 2007; Aybek et al., 2015; Espay et al., 2018b) across FND populations; similar findings have been reported during somatosensory processing in patients with functional numbness (Mailis-Gagnon et al., 2003; Burke et al., 2014). Additionally, other salience network structures are implicated in the pathophysiology of FND, with both rs-FC and task-based fMRI studies identifying altered amygdalar

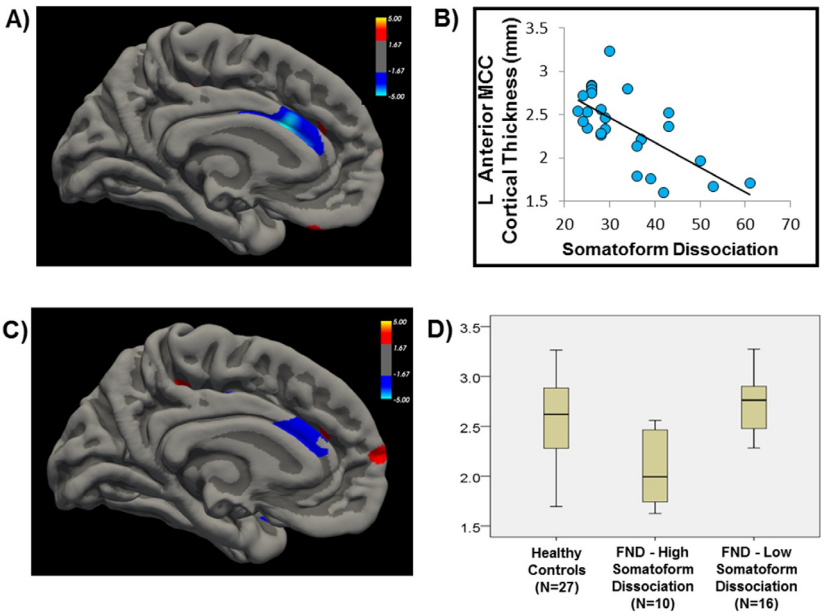

Fig. 14.4. Reduced anterior midcingulate cortex (MCC) cortical thickness linked to somatoform dissociation severity using within-group (panel A) and stratified between-group (panel B) analyses in patients with motor functional neurologic disorders. Images provided courtesy of David Perez and are based on the Perez, D.L., Matin, N., Williams, B., et al., 2018a. Cortical thickness alterations linked to somatoform and psychological dissociation in functional neurological disorders. Hum Brain Mapp 39, 428–439 publication.

(Voon et al., 2011; Ding et al., 2013; Morris et al., 2017; Bègue et al., 2018; Wegrzyk et al., 2018; Diez et al., 2019) and insular (Stone et al., 2007; Czarnecki et al., 2011; Voon et al., 2011; Ding et al., 2013, 2014; Burke et al., 2014; Saj et al., 2014; Nahab et al., 2017; Diez et al., 2019) activity. Importantly, when processing emotionally valenced stimuli, patients with FND display increased amygdalar activity (sensitization and impaired habituation) (Kanaan et al., 2007; Voon et al., 2010a; Aybek et al., 2015; Hassa et al., 2017) and SMA (Aybek et al., 2014, 2015) and PAG (Aybek et al., 2015) activations, along with enhanced amygdala–SMA connectivity (Voon et al., 2010a; Aybek et al., 2014; Hassa et al., 2017). Emerging structural neuroimaging studies in FND also suggest aMCC volumetric alterations (Labate et al., 2012; Perez et al., 2018a) as well as between-group and within-group increases in amygdalar gray matter volumes (Perez et al., 2017b; Maurer et al., 2018). Early evidence implicates that left anterior insular volumetric reductions may be linked to symptom severity, particularly in women (Perez et al., 2017a, b).

The functional and structural alterations found in the ACC can be interpreted in part as related to increased self-monitoring and ACC-mediated motor inhibition (Marshall et al., 1997; van Beilen et al., 2010). In our view, however, the structural and functional alterations in the aMCC may be contextualized through meta-analyses supporting that this area is a cortical hub for the integration of negative affect, pain, and cognitive control (Vogt, 2005; Shackman et al., 2011). Additionally, aMCC plays a role in the appraisal and expression of negative emotion, while the perigenual ACC is involved in emotion regulation via connections to the amygdala, insula, and PAG (Etkin et al., 2011). Notably, impaired top-down perigenual ACC inhibition of amygdalar outflow is a commonly identified corticolimbic alteration across mood- and trauma-related disorders (Etkin, 2010; Lanius et al., 2010). In addition, in patients with FND, PTSD symptom severity correlated inversely with perigenual ACC gray matter volume (Perez et al., 2017a), which is similar to brain-PTSD relationships identified in large-scale studies (Kuhn and Gallinat, 2013). Thus, we speculate that structural and functional alterations in the perigenual/subgenual ACC may be nonspecific for FND and related to mood dysregulation and trauma symptoms, while aMCC alterations may be potentially more specifically related to impaired cognitive control, behavioral expression of mood states, nociception, multimodal integration, and motor control in patients with FND. Presently, more research is needed in larger cohorts to further disentangle these ACC-/MCC-FND relationships.

Insular findings may also be contextualized through the cognitive affective neuroscience literature. Convergent functional neuroimaging studies suggest that the insula mediates aspects of self and emotional awareness; the posterior aspect is responsible for interoceptive representations of the physiologic state of the body

(Craig, 2002), the mid-insula adds emotional salience, and information is integrated in the anterior insula (Paulus and Stein, 2006; Craig, 2009). Notably, early work suggests interoceptive processing deficits in patients with FND (Pick et al., 2017), including one study using a classic heartbeat detection task (Ricciardi et al., 2016). Within this framing, we have previously theorized that cingulo-insular functional and structural alterations may promote failed integration of affective, cognitive, and viscerosomatic information, contributing to a network-mediated "functional unawareness" in patients with FND (Perez et al., 2012, 2015). In support of this possibility, Perez and colleagues have shown that brain–FND symptom severity relationships are linked to left anterior insula gray matter and functional connectivity profiles in patients with FND (Perez et al., 2017a; Diez et al., 2019); in stratified between-group analyses, patients with the greatest impairments in physical health also showed reduced left anterior insular volumes compared to controls (Perez et al., 2017b). Given that these findings have not yet been replicated across FND populations (Maurer et al., 2018), more research is needed to identify the critical nodes in the pathophysiology for functional neurologic symptoms.

Across neuroimaging studies, there is now convergent evidence to suggest an important role for the amygdala in the pathophysiology of FND (Voon et al., 2010a; Aybek et al., 2014, 2015; Hassa et al., 2017; Morris et al., 2017; Perez et al., 2017b; Maurer et al., 2018; Diez et al., 2019). Patients with FND exhibit larger amygdalar volumes (Maurer et al., 2018), with individual differences in amygdalar volumes also linked to elevated trait anxiety and overall impaired mental health (Perez et al., 2017b). Heightened amygdalar activity to emotional stimuli and during motor task performance is well described (Kanaan et al., 2007; Voon et al., 2010a, 2011; Aybek et al., 2015; Hassa et al., 2017; Morris et al., 2017; Bègue et al., 2018; Wegrzyk et al., 2018), as is increased amygdalar-SMA coupling (Voon et al., 2010a; Aybek et al., 2014; Hassa et al., 2017). These findings are consistent with decreased top-down regulatory control of the amygdala via prefrontal connections as discussed earlier. Importantly, the amygdala modulates the PAG, which is closely linked to threat responses including fight or flight and tonic immobility (Roelofs, 2017). Moreover, and consistent with amygdalar/PAG hyperactivations and heightened amygdalar-PAG connectivity (Aybek et al., 2015; Diez et al., 2019), patients with FND exhibit sympathetic hyperarousal and reduced parasympathetic activity. Studies in patients with PNES have shown baseline cortisol elevations and reduced heart rate (HR) variability with pre-ictal HR increases and postictal reductions (Bakvis et al., 2010; Reinsberger et al., 2012). Similarly, mixed FMD cohorts exhibit increased sympathetic tone, including reduced heart rate variability, increased skin conductance, and amplified startle responses (Seignourel et al., 2007; Kozlowska et al., 2015; Pick et al., 2016; Maurer et al., 2016b; Apazoglou et al., 2017; Dreissen et al., 2017). Together these findings point toward a neurobiology of FND that involves aberrant cingulo-insular top-down regulation along with limbic and neuroendocrine system abnormalities.

In addition to the salience network, neurocircuit alterations in FND have also been identified in motor execution, cognitive control, social cognition, and default mode networks (Voon et al., 2016). Also, as previously noted, the right temporoparietal junction plays an important role in impaired self-agency perceptions in patients with FMD (Voon et al., 2010b; Maurer et al., 2016a; Baek et al., 2017). More research is needed, however, to provide specificity to the emerging salience network alterations in FND. Future tasks include (1) delineating which cingulo-insular-amygdalar subregions are specific for the pathophysiology of FND and which areas exhibit changes driven by the affective comorbidities present in FND populations; (2) relating salience network alterations to the nuanced spectrum of predisposing vulnerabilities for the development of FND, including, but not limited to, adverse life event burden (Keynejad et al., 2018; Ludwig et al., 2018), attachment styles, and coping tendencies (Perez et al., 2018b); and (3) identifying biomarkers of prognosis and treatment response (Perez et al., 2018b; Diez et al., 2019).

In conclusion, convergent functional and structural salience network alterations have been linked to the neurobiology of FND. These findings likely relate in part to aberrant emotional processing, arousal, interoception, multimodal integration, self-awareness, and behavioral expression of mood states among other processes.

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DISCLOSURES/CONFLICTS OF INTEREST

None.

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