Published in final edited form as:

Handb Clin Neurol. 2019 ; 166: 267–279. doi:10.1016/B978-0-444-64196-0.00014-5.

The Role of the Anterior and Middle Cingulate Cortices in the Neurobiology of Functional Neurological Disorder

Juan Pablo Ospina¹, Rozita Jalilianhasanpour¹, David L. Perez²

¹Department of Neurology, Cognitive Behavioral Neurology Unit, Functional Neurology Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

²Departments of Neurology and Psychiatry, Cognitive Behavioral Neurology and Neuropsychiatry Units, Functional Neurology Research Group, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Functional neurological 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 neurobiological disease mechanisms. In this review, we summarize the neuroimaging literature across the spectrum of sensorimotor FND, including functional imaging studies during rest, sensorimotor, and emotional processing tasks as well as structural magnetic resonance imaging findings. 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 affectively valenced stimuli, enhanced coupling between amygdalar and motor control areas, and increased amygdalar volumes. The early-phase structural neuroimaging literature 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.

Keywords

functional movement disorders; psychogenic nonepileptic seizures; conversion disorder; neuroimaging; fMRI; cingulate cortex; insula

---

Corresponding Author: David L. Perez, MD MMSc, Address: Massachusetts General Hospital, 55 Fruit Street, Boston, MA, 02114, dlperez@partners.org, Phone: 617-724-7243.

Disclosures/Conflicts of Interest
None

Introduction

Functional neurological disorder (FND) is a common neurobehavioral/ neuropsychiatric condition defined by neurological symptoms that are not explained by other medical-neurological conditions, and encompasses functional weakness (FW), functional movement disorders (FMD), psychogenic non-epileptic seizures (PNES, also known as dissociative seizures), functional speech, and/or non-dermatomal sensory deficits (functional numbness) (Espay et al., 2018a). With the Diagnostic and Statistical Manual of Mental Disorders - 5th Edition, FND was redefined as a “rule-in” condition based on neurological exam signs, removing the need to identify a proximal stressor or exclude malingering (Stone et al., 2010b; Stone et al., 2011). Importantly, FND is the second most common referral to outpatient neurology (Stone et al., 2010a), and medically unexplained symptoms 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 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 (Perez et al., 2012; Kanaan et al., 2009).

Clinical and neurobiological 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; Keynejad et al., 2018; Perez et al., 2017a), although not all individuals with FND endorse prior traumatic experiences. A recent meta-analysis 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 multi-network problem (Szaflarski and LaFrance, 2018; Aybek and Vuilleumier, 2016), structural and functional neuroimaging studies highlight important links between FND and alterations in the anterior cingulate cortex (ACC), middle cingulate 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 neurobiological 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 article (Spence et al., 2000; Stone et al., 2007; Cojan et al., 2009). Thereafter, we contextualize functional and structural salience

network alterations as linked, in part, to disturbances in multimodal integration, self/emotional awareness, emotion processing/regulation, interoception, and defensive behaviors (Pick et al., 2018).

Review

1. Task-based neuroimaging

1a. 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., 1997b). 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 (Voon et al., 2010b; Czarnecki et al., 2011; Voon et al., 2011; Stone et al., 2007; de Lange et al., 2007; Saj et al., 2014; Van Beilen et al., 2011). Voon, Hallett, and colleagues examined 8 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 complimentary seed-based connectivity analysis displayed decreased coupling between the right TPJ and bilateral sensorimotor cortices, subgenual ACC (sgACC), 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 under-reported 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 contrast revealed perigenual ACC (pgACC) 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 6 patients with functional dystonia to 6 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(Voon et al., 2011; Schrag et al., 2013; Czarnecki et al., 2011) 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 4 patients with functional leg weakness probed activations during leg movements(Stone et al., 2007). During attempted movements of the weak vs. non-affected limb, patients displayed increased basal ganglia, lingual gyri, and inferior frontal cortex activations, along with decreased right prefrontal cortex activations. Although exploratory, uncorrected analyses revealed increased bilateral insula activity. Another study in 8 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 pgACC) and dorsomedial prefrontal activity. Another study of 2 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 patients during movements of their affected limb 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 meta-cognitive abilities in 10 patients with mixed sensorimotor FND vs. HCs attempting to draw straight lines towards 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), preSMA, 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., 1997b; Czarnecki et al., 2011; Voon et al., 2011; de Lange et al., 2007; Van Beilen et al., 2011; Nahab et al., 2017; Bègue et al., 2018; Saj et al., 2014), as well as areas involved in self-agency perception (right TPJ)(Voon et al., 2010b; Nahab et al., 2017; Schrag et al., 2013), during performance of motor behaviors. Several studies have characterized cingulo-insular (including pgACC and MCC) hyperactivations during motor tasks(de Lange et al., 2007; Marshall et al., 1997a; Saj et al., 2009; Voon et al., 2011; Van Beilen et al., 2011), although the directionality of these findings has not been consistent across all studies(Czarnecki et al., 2011; Schrag et al., 2013).

1b. sensory processing tasks—fMRI studies applying tactile stimuli to individuals with non-dermatomal sensory deficits also highlight a role for the ACC and MCC in the pathophysiology of functional numbness (Mailis-Gagnon et al., 2003; Burke et al., 2014; Saj et al., 2009). One report examined 4 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 pgACC, 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 towards ACC/MCC alterations in individuals experiencing functional somatosensory deficits, however, more research is needed to determine sub-region specificity and the directionality of findings.

1c. emotion processing tasks—Several studies have used affectively valenced probes to investigate emotion processing in patients with FND, identifying increased amygdalar and related salience network activity (Kanaan et al., 2007; Aybek et al., 2014; Voon et al., 2010a; Aybek et al., 2015; Hassa et al., 2017; Espay et al., 2018c; Espay et al., 2018b; Pick et al., 2018). 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 affectively valenced 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 affectively valenced stimuli. Another study employing affectively 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 Figure 1). A more recent study probed motor - emotion processing in 13 patients with FW compared to HCs using a dual passive movement and

implicit affectively 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(Aybek et al., 2014; Voon et al., 2010a), 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 affectively-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 affectively-valenced 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; Aybek et al., 2014; Voon et al., 2010a; Aybek et al., 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; Aybek et al., 2015; Espay et al., 2018b; Espay et al., 2018c).

2. Resting-state functional connectivity findings in FND

Resting-state functional connectivity (rs-FC) techniques have also been applied to investigate neurocircuit 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; Szaflarski et al., 2018; Li et al., 2015b; Li et al., 2015a; Morris et al., 2017; van der Kruijs et al., 2014; Ding et al., 2013; Arthuis et al., 2015), as well as more widely distributed alterations within sensorimotor, executive control and default mode networks(Maurer et al., 2016a; Ding et al., 2014).

2.a 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 (pgACC, 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 pgACC, the insula, and left precentral sulcus. Additionally, higher 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 affectively-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 positively correlated with seizure frequency. Another study also showed that ACC - SMA connectivity strength positively correlated 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 was 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, patients with FND exhibited increased link-step connectivity from primary motor cortex to bilateral MCC and right TPJ

compared to controls; patients with FND also showed enhanced motor cortex to posterior insula functional propagation that did not remain significant adjusting for depression and anxiety. From the right laterobasal amygdala, patients with FND showed increased functional propagation to the left anterior insula, PAG and hypothalamus compared to controls (results did not hold adjusting for depression/anxiety). The flow of information from the left anterior insula to the right anterior insula, TPJ, precentral gyrus and SMA positively correlated with patient-reported symptom severity adjusting for individual differences in depression and anxiety scores.

As a follow-up to earlier work by Voon, Hallett and colleagues (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 feed-forward processing (sensorimotor – right TPJ connectivity) and right TPJ – left insular connectivity as implicated in impaired awareness in patients with FMD.

2.b 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 sgACC 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 co-activations 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; Ding et al., 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. Intra-network 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 temporo-parietal (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 Figure 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 towards alterations in neurocircuits 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.

3. 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, superior frontal gyri, and precuneus in individuals with PNES compared to controls. In within-group analyses, left inferior frontal cortical thickness negatively correlated with somatoform dissociation scores. Another cortical thickness study in 37 patients with PNES and 37 HCs (Risti 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, 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; Perez et al., 2017b). 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 negatively correlated with patient-reported symptom severity in the subset of 18 women with FND. Additionally, childhood abuse burden negatively correlated with left anterior insular volumes in women with FND, and adverse life event burden across the lifespan correlated with reduced left hippocampal volumes across all patients. Furthermore, post-traumatic stress disorder (PTSD) symptom severity inversely related to pgACC 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 Figure 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 analyses, the same group have also examined associations between somatoform and psychological 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 inversely correlated with somatoform dissociation scores across the entire FND cohort (See Figure 4). In post-hoc analyses, this finding remained significant controlling for anxiety/depression, borderline personality disorder, PTSD, adverse life events and FND subtype.

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(Maurer et al., 2018; Perez et al., 2017b). Moreover, early work suggests possible important correlations between volumetric alterations in salience network structures and markers of symptom severity(Perez et al., 2017a; Perez et al., 2017b; Labate et al., 2012; Perez et al., 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; Perez et al., 2015). Several PET studies have reported altered perfusion or metabolism in the ACC/aMCC across patients with FW, FMD, and PNES during rest and movement(Marshall et al., 1997b; 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., 2014; van der Kruijs et al., 2012). 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 (Voon et al., 2011; Bègue et al., 2018; Morris et al., 2017; Ding et al., 2013; Wegrzyk et al., 2018; Diez et al., 2019) and insular (Stone et al., 2007; Czarnecki et al., 2011; Voon et al., 2011; Nahab et al., 2017; Burke et al., 2014; Ding et al., 2013; Ding et al., 2014; Saj et al., 2014; 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), SMA (Aybek et al., 2014; Aybek et al., 2015) and PAG (Aybek et al., 2015) activations, along with enhanced amygdala – SMA connectivity (Aybek et al., 2014; Hassa et al., 2017; Voon et al., 2010a). 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 (Maurer et al., 2018; Perez et al., 2017b). Early evidence implicates that left anterior insular volumetric reductions may be linked to symptom severity, particularly in women (Perez et al., 2017b; Perez et al., 2017a).

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., 1997b; 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 hub for the integration of negative affect, pain, and cognitive control (Shackman et al., 2011; Vogt, 2005). 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 the 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 (Lanius et al., 2010; Etkin, 2010). In addition, in patients with FND, PTSD symptom severity inversely correlated 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 non-specific 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, where the posterior aspect is responsible for

interoceptive representations of the physiological state of the body (Craig, 2002), the mid-insula adds emotional salience, and information is integrated in the anterior insula (Craig, 2009; Paulus and Stein, 2006). Notably, early work suggest interoceptive processing deficits in patients with FND (Pick et al., 2017), including one study using a classic heart beat 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; Perez et al., 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 neurological symptoms.

Across neuroimaging studies, there is now convergent evidence to suggest an important role for the amygdala in the pathophysiology of FND (Maurer et al., 2018; Perez et al., 2017b; Hassa et al., 2017; Voon et al., 2010a; Aybek et al., 2014; Morris et al., 2017; Aybek et al., 2015; 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 (Voon et al., 2011; Bègue et al., 2018; Morris et al., 2017; Wegrzyk et al., 2018; Kanaan et al., 2007; Voon et al., 2010a; Aybek et al., 2015; Hassa et al., 2017), as well as increased amygdalar-SMA coupling (Aybek et al., 2014; Hassa et al., 2017; Voon et al., 2010a). These findings are consistent with decreased top-down regulatory control of the amygdala via prefrontal connections as discussed above. 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, patients with FND exhibit sympathetic hyperarousal and reduced parasympathetic activity (Aybek et al., 2015; Diez et al., 2019). 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 (Apazoglou et al., 2017; Maurer et al., 2016b; Kozłowska et al., 2015; Pick et al., 2016; Seignourel et al., 2007; Dreissen et al., 2017). Together these findings point towards a neurobiology of FND that involves aberrant cingulo-insular top-down regulation along with limbic and neuroendocrine system hyperactivations.

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; Baek et

al., 2017; Maurer et al., 2016a). 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 co-morbidities 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); 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/regulation, arousal, interoception, multimodal integration, self-awareness and behavioral expression of mood states among other processes.

Acknowledgements

The authors would like to thank Selma Aybek, Timothy Nicholson, Eric Guedj and Aileen McGonigal for providing images of their research.

Funding

D.L.P. was funded by the NIMH K23MH111983-02, Sidney R. Baer Jr. Foundation and the Massachusetts General Hospital Physician-Scientist Career Development Award.

References:

- Apazoglou K, Mazzola V, Wegrzyk J, et al. (2017). Biological and perceived stress in motor functional neurological disorders. *Psychoneuroendocrinology* 85: 142–150. [PubMed: 28863348]
- Arthuis M, Micoulaud-Franchi JA, Bartolomei F, et al. (2015). Resting cortical PET metabolic changes in psychogenic non-epileptic seizures (PNES). *J Neurol Neurosurg Psychiatry* 86: 1106–1112. [PubMed: 25466258]
- Aybek S, Nicholson TR, O'Daly O, et al. (2015). Emotion-motion interactions in conversion disorder: an fMRI study. *PLoS One* 10: e0123273.
- Aybek S, Nicholson TR, Zelaya F, et al. (2014). Neural correlates of recall of life events in conversion disorder. *JAMA Psychiatry* 71: 52–60. [PubMed: 24258270]
- Aybek S & Vuilleumier P (2016). Imaging studies of functional neurologic disorders. *Handb Clin Neurol* 139: 73–84. [PubMed: 27719879]
- Baek K, Doñamayor N, Morris LS, et al. (2017). Impaired awareness of motor intention in functional neurological disorder: Implications for voluntary and functional movement. *Psychological Medicine* 47: 1624–1636. [PubMed: 28183377]
- Bakvis P, Spinhoven P, Giltay EJ, et al. (2010). Basal hypercortisolism and trauma in patients with psychogenic nonepileptic seizures. *Epilepsia* 51: 752–759. [PubMed: 19889016]
- Barsky AJ, Orav EJ & Bates DW (2005). Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch Gen Psychiatry* 62: 903–910. [PubMed: 16061768]
- Bègue I, Blakemore R, Klug J, et al. (2018). Metacognition of visuomotor decisions in conversion disorder. *Neuropsychologia* 114: 251–265. [PubMed: 29698734]
- Burke MJ, Ghaffar O, Staines WR, et al. (2014). Functional neuroimaging of conversion disorder: the role of ancillary activation. *Neuroimage Clin* 6: 333–339. [PubMed: 25379447]

- Cojan Y, Waber L, Schwartz S, et al. (2009). The brain under self-control: modulation of inhibitory and monitoring cortical networks during hypnotic paralysis. *Neuron* 62: 862–875. [PubMed: 19555654]
- Craig AD (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 3: 655–666. [PubMed: 12154366]
- Craig AD (2009). How do you feel--now? The anterior insula and human awareness. *Nat Rev Neurosci* 10: 59–70. [PubMed: 19096369]
- Czarnecki K, Jones DT, Burnett MS, et al. (2011). SPECT perfusion patterns distinguish psychogenic from essential tremor. *Parkinsonism Relat Disord* 17: 328–332. [PubMed: 21317018]
- de Lange FP, Roelofs K & Toni I (2007). Increased self-monitoring during imagined movements in conversion paralysis. *Neuropsychologia* 45: 2051–2058. [PubMed: 17367826]
- Desmurget M, Reilly KT, Richard N, et al. (2009). Movement intention after parietal cortex stimulation in humans. *Science* 324: 811–813. [PubMed: 19423830]
- Diez I, Ortiz-Teran L, Williams B, et al. (2019). Corticolimbic fast-tracking: enhanced multimodal integration in functional neurological disorder. *J Neurol Neurosurg Psychiatry*.
- Ding J-R, An D, Liao W, et al. (2013). Altered functional and structural connectivity networks in psychogenic non-epileptic seizures. *PloS one* 8: e63850.
- Ding J, An D, Liao W, et al. (2014). Abnormal functional connectivity density in psychogenic non-epileptic seizures. *Epilepsy Res* 108: 1184–1194. [PubMed: 24974125]
- Dreissen YEM, Boeree T, Koelman J, et al. (2017). Startle responses in functional jerky movement disorders are increased but have a normal pattern. *Parkinsonism Relat Disord* 40: 27–32. [PubMed: 28410805]
- Espay AJ, Aybek S, Carson A, et al. (2018a). Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders. *JAMA Neurol* 75: 1132–1141. [PubMed: 29868890]
- Espay AJ, Maloney T, Vannest J, et al. (2018b). Dysfunction in emotion processing underlies functional (psychogenic) dystonia. *Movement Disorders* 33: 136–145. [PubMed: 29124784]
- Espay AJ, Maloney T, Vannest J, et al. (2018c). Impaired emotion processing in functional (psychogenic) tremor: A functional magnetic resonance imaging study. *NeuroImage: Clinical* 17: 179–187. [PubMed: 29085776]
- Etkin A (2010). Functional neuroanatomy of anxiety: a neural circuit perspective. *Curr Top Behav Neurosci* 2: 251–277. [PubMed: 21309113]
- Etkin A, Egner T & Kalisch R (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends Cogn Sci* 15: 85–93. [PubMed: 21167765]
- Hassa T, Sebastian A, Liepert J, et al. (2017). Symptom-specific amygdala hyperactivity modulates motor control network in conversion disorder. *NeuroImage: Clinical* 15: 143–150. [PubMed: 28529870]
- Jones B, Reuber M & Norman P (2016). Correlates of health-related quality of life in adults with psychogenic nonepileptic seizures: A systematic review. *Epilepsia* 57: 171–181. [PubMed: 26701628]
- Kanaan R, Armstrong D, Barnes P, et al. (2009). In the psychiatrist's chair: how neurologists understand conversion disorder. *Brain* 132: 2889–2896. [PubMed: 19321463]
- Kanaan RA, Craig TK, Wessely SC, et al. (2007). Imaging repressed memories in motor conversion disorder. *Psychosomatic Medicine* 69: 202–205. [PubMed: 17327215]
- Keynejad RC, Frodl T, Kanaan R, et al. (2018). Stress and functional neurological disorders: mechanistic insights. *J Neurol Neurosurg Psychiatry*.
- Kozłowska K, Palmer DM, Brown KJ, et al. (2015). Reduction of autonomic regulation in children and adolescents with conversion disorders. *Psychosom Med* 77: 356–370. [PubMed: 25954919]
- Kuhn S & Gallinat J (2013). Gray matter correlates of posttraumatic stress disorder: a quantitative meta-analysis. *Biol Psychiatry* 73: 70–74. [PubMed: 22840760]
- Labate A, Cerasa A, Mula M, et al. (2012). Neuroanatomic correlates of psychogenic nonepileptic seizures: a cortical thickness and VBM study. *Epilepsia* 53: 377–385. [PubMed: 22150750]

- Lanius RA, Vermetten E, Loewenstein RJ, et al. (2010). Emotion modulation in PTSD: Clinical and neurobiological evidence for a dissociative subtype. *Am J Psychiatry* 167: 640–647. [PubMed: 20360318]
- Li R, Li Y, An D, et al. (2015a). Altered regional activity and inter-regional functional connectivity in psychogenic non-epileptic seizures. *Scientific reports* 5: 11635.
- Li R, Liu K, Ma X, et al. (2015b). Altered functional connectivity patterns of the insular subregions in psychogenic nonepileptic seizures. *Brain topography* 28: 636–645. [PubMed: 25352166]
- Ludwig L, Pasman JA, Nicholson T, et al. (2018). Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. *Lancet Psychiatry* 5: 307–320. [PubMed: 29526521]
- Mailis-Gagnon A, Giannoylis I, Downar J, et al. (2003). Altered central somatosensory processing in chronic pain patients with “hysterical” anesthesia. *Neurology* 60: 1501–1507. [PubMed: 12743239]
- Marshall JC, Halligan PW, Fink GR, et al. (1997a). The functional anatomy of a hysterical paralysis. *Cognition* 64: B1–8. [PubMed: 9342933]
- Marshall JC, Halligan PW, Fink GR, et al. (1997b). The functional anatomy of a hysterical paralysis. *Cognition* 64: B1–B8. [PubMed: 9342933]
- Maurer CW, LaFaver K, Ameli R, et al. (2016a). Impaired self-agency in functional movement disorders: a resting-state fMRI study. *Neurology*: 10.1212/WNL.0000000000002940.
- Maurer CW, LaFaver K, Limachia GS, et al. (2018). Gray matter differences in patients with functional movement disorders. *Neurology* 91: e1870–e1879. [PubMed: 30305450]
- Maurer CW, Liu VD, LaFaver K, et al. (2016b). Impaired resting vagal tone in patients with functional movement disorders. *Parkinsonism Relat Disord* 30: 18–22. [PubMed: 27334304]
- McKee K, Glass S, Adams C, et al. (2018). The Inpatient Assessment and Management of Motor Functional Neurological Disorders: An Interdisciplinary Perspective. *Psychosomatics* 59: 358–368. [PubMed: 29628294]
- Monsa R, Peer M & Arzy S (2018). Self-reference, emotion inhibition and somatosensory disturbance: preliminary investigation of network perturbations in conversion disorder. *European journal of neurology* 25: 888–e862.
- Morris LS, To B, Baek K, et al. (2017). Disrupted avoidance learning in functional neurological disorder: Implications for harm avoidance theories. *Neuroimage Clin* 16: 286–294. [PubMed: 28856091]
- Nahab FB, Kundu P, Maurer C, et al. (2017). Impaired sense of agency in functional movement disorders: An fMRI study. *PLOS ONE* 12: e0172502.
- Paulus MP & Stein MB (2006). An insular view of anxiety. *Biol Psychiatry* 60: 383–387. [PubMed: 16780813]
- Perez DL, Barsky AJ, Daffner K, et al. (2012). Motor and somatosensory conversion disorder: a functional unawareness syndrome? *J Neuropsychiatry Clin Neurosci* 24: 141–151. [PubMed: 22772662]
- Perez DL, Dworetzky BA, Dickerson BC, et al. (2015). An integrative neurocircuit perspective on psychogenic nonepileptic seizures and functional movement disorders: neural functional unawareness. *Clin EEG Neurosci* 46: 4–15. [PubMed: 25432161]
- Perez DL, 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. [PubMed: 28416565]
- Perez DL, 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. [PubMed: 29080235]
- Perez DL, Williams B, Matin N, et al. (2017b). Corticolimbic structural alterations linked to health status and trait anxiety in functional neurological disorder. *J Neurol Neurosurg Psychiatry* 88: 1052–1059. [PubMed: 28844071]
- Perez DL, Williams B, Matin N, et al. (2018b). Anterior hippocampal grey matter predicts mental health outcome in functional neurological disorders: an exploratory pilot study. *J Neurol Neurosurg Psychiatry*.

- Pick S, Goldstein LH, Perez DL, et al. (2018). Emotional processing in functional neurological disorder: a review, biopsychosocial model and research agenda. *J Neurol Neurosurg Psychiatry*.
- Pick S, Mellers JD & Goldstein LH (2016). Explicit Facial Emotion Processing in Patients With Dissociative Seizures. *Psychosom Med* 78: 874–885. [PubMed: 27187848]
- Pick S, Mellers JDC & Goldstein LH (2017). Autonomic and subjective responsivity to emotional images in people with dissociative seizures. *J Neuropsychol*.
- Reinsberger C, Perez DL, Murphy MM, et al. (2012). Pre- and postictal, not ictal, heart rate distinguishes complex partial and psychogenic nonepileptic seizures. *Epilepsy Behav* 23: 68–70. [PubMed: 22100065]
- Ricciardi L, Demartini B, Crucianelli L, et al. (2016). Interoceptive awareness in patients with functional neurological symptoms. *Biological psychology* 113: 68–74. [PubMed: 26528552]
- Risti AJ, Dakovi M, Kerr M, et al. (2015). Cortical thickness, surface area and folding in patients with psychogenic nonepileptic seizures. *Epilepsy research* 112: 84–91. [PubMed: 25847343]
- Roelofs K (2017). Freeze for action: neurobiological mechanisms in animal and human freezing. *Philos Trans R Soc Lond B Biol Sci* 372.
- Roelofs K, Keijsers GP, Hoogduin KA, et al. (2002). Childhood abuse in patients with conversion disorder. *Am J Psychiatry* 159: 1908–1913. [PubMed: 12411227]
- Saj A, Arzy S & Vuilleumier P (2009). Functional brain imaging in a woman with spatial neglect due to conversion disorder. *JAMA* 302: 2552–2554.
- Saj A, Raz N, Levin N, et al. (2014). Disturbed mental imagery of affected body-parts in patients with hysterical conversion paraplegia correlates with pathological limbic activity. *Brain Sci* 4: 396–404. [PubMed: 24961768]
- Schrag AE, Mehta AR, Bhatia KP, et al. (2013). The functional neuroimaging correlates of psychogenic versus organic dystonia. *Brain* 136: 770–781. [PubMed: 23436503]
- Seeley WW, Menon V, Schatzberg AF, et al. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *J Neurosci* 27: 2349–2356. [PubMed: 17329432]
- Seignourel PJ, Miller K, Kellison I, et al. (2007). Abnormal affective startle modulation in individuals with psychogenic [corrected] movement disorder. *Mov Disord* 22: 1265–1271. [PubMed: 17486611]
- Selkirk M, Duncan R, Oto M, et al. (2008). Clinical differences between patients with nonepileptic seizures who report antecedent sexual abuse and those who do not. *Epilepsia* 49: 1446–1450. [PubMed: 18410361]
- Shackman AJ, Salomons TV, Slagter HA, et al. (2011). The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci* 12: 154–167. [PubMed: 21331082]
- Spence SA, Crimlisk HL, Cope H, et al. (2000). Discrete neurophysiological correlates in prefrontal cortex during hysterical and feigned disorder of movement. *Lancet* 355: 1243–1244. [PubMed: 10770312]
- Stone J, Carson A, Duncan R, et al. (2010a). Who is referred to neurology clinics?--the diagnoses made in 3781 new patients. *Clin Neurol Neurosurg* 112: 747–751. [PubMed: 20646830]
- Stone J, LaFrance WC Jr., Brown R, et al. (2011). Conversion disorder: current problems and potential solutions for DSM-5. *J Psychosom Res* 71: 369–376. [PubMed: 22118377]
- Stone J, LaFrance WC Jr., Levenson JL, et al. (2010b). Issues for DSM-5: Conversion disorder. *Am J Psychiatry* 167: 626–627. [PubMed: 20516161]
- Stone J, Zeman A, Simonotto E, et al. (2007). fMRI in patients with motor conversion symptoms and controls with simulated weakness. *Psychosom Med* 69: 961–969. [PubMed: 17991812]
- Szaflarski JP, Allendorfer JB, Nenert R, et al. (2018). Facial emotion processing in patients with seizure disorders. *Epilepsy & Behavior* 79: 193–204. [PubMed: 29309953]
- Szaflarski JP & LaFrance WC Jr., (2018). Psychogenic Nonepileptic Seizures (PNES) as a Network Disorder - Evidence From Neuroimaging of Functional (Psychogenic) Neurological Disorders. *Epilepsy Curr* 18: 211–216. [PubMed: 30254510]
- Van Beilen M, De Jong BM, Gieteling EW, et al. (2011). Abnormal parietal function in conversion paresis. *PLoS One* 6: e25918.

- van Beilen M, Vogt BA & Leenders KL (2010). Increased activation in cingulate cortex in conversion disorder: what does it mean? *J Neurol Sci* 289: 155–158. [PubMed: 19733363]
- van der Kruijs SJ, Bodde NM, Vaessen MJ, et al. (2012). Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 83: 239–247. [PubMed: 22056967]
- van der Kruijs SJ, Jagannathan SR, Bodde NM, et al. (2014). Resting-state networks and dissociation in psychogenic non-epileptic seizures. *J Psychiatr Res* 54: 126–133. [PubMed: 24703187]
- Vogt BA (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 6: 533–544. [PubMed: 15995724]
- Vogt BJ (2019). The cingulate cortex in neurological diseases: the silent administrator. *Handb Clin Neurol* 166: 1–21.
- Voon V, Brezing C, Gallea C, et al. (2010a). Emotional stimuli and motor conversion disorder. *Brain* 133: 1526–1536. [PubMed: 20371508]
- Voon V, Brezing C, Gallea C, et al. (2011). Aberrant supplementary motor complex and limbic activity during motor preparation in motor conversion disorder. *Mov Disord* 26: 2396–2403. [PubMed: 21935985]
- Voon V, Cavanna AE, Coburn K, et al. (2016). Functional Neuroanatomy and Neurophysiology of Functional Neurological Disorders (Conversion Disorder). *J Neuropsychiatry Clin Neurosci* 28: 168–190. [PubMed: 26900733]
- Voon V, Gallea C, Hattori N, et al. (2010b). The involuntary nature of conversion disorder. *Neurology* 74: 223–228. [PubMed: 20083798]
- Wegrzyk J, Kebets V, Richiardi J, et al. (2018). Identifying motor functional neurological disorder using resting-state functional connectivity. *NeuroImage: Clinical* 17: 163–168. [PubMed: 29071210]

Figure 1. Hyperactivation of the amygdala (panel A), anterior middle cingulate cortex (panel B) and periaqueductal gray (panel C) in patients with motor functional neurological disorder compared to controls during affectively valenced face processing. Images provided courtesy of Selma Aybek and Timothy Nicholson, and are based on the Aybek et al. (2015) publication(Aybek et al., 2015).

Figure 2. Hypometabolism of the anterior cingulate and anterior middle cingulate 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 et al. (2015) publication(Arthuis et al., 2015).

Figure 3.

Women with motor functional neurological 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 (ACC) gray matter volumes. Images provided courtesy of David Perez, and are based on the Perez et al. (2017a) publication(Perez et al., 2017a).

Figure 4. Reduced anterior middle cingulate 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 neurological disorders. Images provided courtesy of David Perez, and are based on the Perez et al. (2018a) publication(Perez et al., 2018a).