



## Grey matter abnormalities in children and adolescents with functional neurological symptom disorder



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### ABSTRACT

**Objective:** Functional neurological symptom disorder refers to the presence of neurological symptoms not explained by neurological disease. Although this disorder is presumed to reflect abnormal *function* of the brain, recent studies in adults show neuroanatomical abnormalities in brain *structure*. These structural brain abnormalities have been presumed to reflect long-term adaptations to the disorder, and it is unknown whether child and adolescent patients, with illness that is typically of shorter duration, show similar deficits or have normal brain structure.

**Method:** High-resolution, three-dimensional T1-weighted magnetic resonance images (MRIs) were acquired in 25 patients (aged 10–18 years) and 24 healthy controls. Structure was quantified in terms of grey matter volume using voxel-based morphometry. Post hoc, we examined whether regions of structural difference related to a measure of motor readiness to emotional signals and to clinical measures of illness duration, illness severity, and anxiety/depression.

**Results:** Patients showed greater volumes in the left supplementary motor area (SMA) and right superior temporal gyrus (STG) and dorsomedial prefrontal cortex (DMPFC) (corrected  $p < 0.05$ ). Previous studies of adult patients have also reported alterations of the SMA. Greater SMA volumes correlated with faster reaction times in identifying emotions but not with clinical measures.

**Conclusions:** The SMA, STG, and DMPFC are known to be involved in the perception of emotion and the modulation of motor responses. These larger volumes may reflect the early expression of an experience-dependent plasticity process associated with increased vigilance to others' emotional states and enhanced motor readiness to organize self-protectively in the context of the long-standing relational stress that is characteristic of this disorder.

### 1. Introduction

Functional neurological symptom disorder (FND) involves disturbances of body function characterized by neurological symptoms, either sensory or motor, not explained by neurological disease. Patients with FND present with many diverse symptoms, including psychogenic non-epileptic seizures (PNES); positive movements such as tremor, dystonia, or gait abnormalities; loss of motor function such as leg or arm paresis; and loss of sensory functions such as blindness, deafness, or loss of feeling in the limbs. Presentations in children/adolescents are typically

complicated by high rates of comorbidity between functional neurological symptoms and anxiety, depression, functional pain, and non-specific somatic symptoms (Ani et al., 2013; Kozłowska et al., 2011; Kozłowska et al., 2013c).

In the 1800s, well before the advent of neuroimaging technologies, prominent clinicians such as Briquet, Charcot, and Janet hypothesized that functional neurological disorders were, at least in part, the product of a weak nervous constitution or weakened integrative capacity that involved subtle structural changes that could not be identified using the anatomical methodologies of the time (Briquet, 1859; Charcot, 1889;

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Janet, 1889). More recently, the major classificatory systems—*International Classification of Diseases* and *Diagnostic and Statistical Manual of Mental Disorders* (DSM)—have moved away from the idea of subtle structural changes and have conceptualized FND as a functional disorder, one that is not accounted for by the presence of structural abnormalities. In line with this framework, functional metaphors are often used when discussing FND with patients and their families. Symptoms may be framed as a “software” rather than a “hardware” problem, reflecting the idea that the neural system is structurally sound but is not functioning properly. In the clinical setting, the widespread use of computerized axial tomography (CT) and magnetic resonance imaging (MRI) on an individual level of analysis has failed to disclose any structural abnormalities, thereby supporting the classification of FND as functional disorder. Even when a comorbid structural abnormality is found, it is not located in a region that would account for the patient's pattern of neurological impairment.

More recently, the debate about structural changes in FND has been rekindled. Recent studies using group-level analyses in adult patients with FND have found structural differences in motor-processing regions or in motor regions with dual motor-processing and emotion-processing functions. In patients with chronic psychogenic non-epileptic seizures, decreased grey matter has been reported in the right motor and premotor regions and in the bilateral cerebellum (Labate et al., 2012). The cerebellum has a dual role in motor coordination and emotion processing (Snow et al., 2014), with functional abnormalities documented in patients with functional dystonia (Schrag et al., 2013) and, during an emotional-force control task, in those with functional motor symptoms (Blakemore et al., 2016). Larger grey matter volumes in the bilateral premotor cortex have been reported in patients exhibiting functional motor hemiparesis (Aybek et al., 2014a; Atmaca et al.), and reduced grey matter volumes in the bilateral caudate, lentiform nuclei, and thalamus were found in patients with motor weakness (Nicholson et al., 2014). Studies in patients with functional unilateral motor loss have also found hypoactivation in the basal ganglia (especially the caudate nucleus) and thalamus, suggesting functional abnormalities in cortico-striato-thalamo-cortical circuits in FND (Vuilleumier et al., 2001). These motor circuits receive converging inputs from the emotion-processing prefrontal and limbic regions, including the orbitofrontal cortex, cingulate, and amygdala, with the result that signals from these regions facilitate, inhibit, or distort patterns of motor activity (Mogenson and Yang, 1991; Haber, 2003; Vuilleumier and Cojan, 2011).

The structural findings in adult patients, as described above, may reflect the experience-dependent, neuroplastic properties of the brain—either its capacity to change in response to repeated stimuli or the lack thereof (e.g., in the wake of prolonged limb immobilization) (Langer et al., 2012). Along these lines, in adult patients with FND, associations between structural changes and clinical measures of symptom severity, illness duration, or depressive symptoms have been reported. Labate et al. (2012) found a positive association between decreased grey matter in the right premotor cortex and depression scores in patients with PNES. Aybek et al. (2014a) found trends of positive correlations between greater grey matter in the left premotor cortex and the degree of functional impairment in patients with motor loss, and also between greater grey matter in the bilateral supplementary motor area (SMA) and illness duration. Taken together, these associations suggest that structural differences may reflect a secondary plasticity phenomenon as a consequence of chronic illness and functional impairment. It is uncertain, however, at which point these structural alterations may first occur—which highlights the need for neuroimaging studies with younger patients, prior to the impact of chronicity on the clinical picture (Aybek et al., 2014a; Nicholson et al., 2014).

An important difference between the clinical presentations of paediatric and adult patients with FND relates to stress. Whereas the role of stress in adult patients is a point of ongoing debate, research

with paediatric patients suggests that FND arises when antecedent stressors—illness, injury, psychological trauma, or emotional distress secondary to life events—lead the child/adolescent's biological system to shift to a brain-body state of higher arousal and motor readiness. Neural, physiological, behavioural, and linguistic (attachment) markers of this shift in brain-body state include the following: higher heart rate and lower heart rate variability (Kozłowska et al., 2015a), greater stimulus elicited neurocortical activity in response to auditory stimuli (Kozłowska et al., 2017a); greater vigilance to, and motor readiness to respond to, emotional signals communicated by facial expressions (emotion-identification reaction times) (Kozłowska et al., 2013a); use of at-risk attachment strategies (Kozłowska et al., 2011); and impairment of the higher cognitive functions mediated by the prefrontal cortex (PFC) (Kozłowska et al., 2015b), consistent with an activation of brain-arousal systems (Arnsten, 2009). An additional finding in paediatric patients who have PNES is that higher arousal is coupled with excessive activation and reactivity of the motor-respiratory system (Kozłowska et al., 2017b).

The present study utilized voxel-based morphometry (VBM) to investigate brain structure in a group of children/adolescents presenting with acute FND using a region-of-interest (ROI) analysis to examine brain regions that differ in adult FND, followed by an exploratory whole-brain analysis. Our goal was to examine the contemporary conceptualization that FND is a functional neurological disorder not explained by changes in brain structure. Because the structural brain differences identified in adult patients are presumed to reflect a secondary plasticity phenomenon as a consequence of chronic illness and functional impairment, and because our paediatric patients had been premorbidly well and had short illness duration, we did not expect them to show the structural brain differences found in adult patients. In this context we hypothesized that our paediatric cohort would not show any of the structural differences identified in adult patients, and we expected that their brain structure would be indistinguishable from healthy controls.

## 2. Methods

### 2.1. Participants

Twenty-nine children and adolescents with FND were recruited from consecutive referrals to the first author's consultation-liaison psychiatry team at a tertiary-care paediatric hospital during the period October 2009 to May 2014. Participants were diagnosed according to modified DSM-IV-TR criteria (American Psychiatric, 2000), whilst DSM-5 criteria were being developed. Consistent with DSM-5 criteria, we did not adhere to the DSM-IV-TR “psychological stressor criterion,” because our previous research with children/adolescents had highlighted that the psychological-stressor criterion was too narrow (Kozłowska et al., 2007; Kozłowska et al., 2011). Instead, we documented, if present, any antecedent stressors—both psychological and physical. Again, in keeping with DSM-5 criteria, all participants had documented positive signs on neurological examination, plus a worsening of symptoms with attention and a decrease of symptoms when distracted by schoolwork and other activities during family assessment, individual assessment, and the inpatient admission. Two boys were excluded from MRI analysis due to movement artefacts, and two girls were excluded because of preexisting neurological MRI abnormalities (cerebral palsy and intracranial hypertension).

All children/adolescents had undergone a comprehensive neurology assessment—which included video electroencephalogram (vEEG) for those with PNES—and diagnosis by a paediatric neurologist. Subsequent to the neurology assessment, all patients and their families attended a psychological medicine family assessment. At that assessment the diagnosis of FND was confirmed by a psychiatrist, a detailed history of the presenting symptoms—including antecedent events—was collected (Kozłowska et al., 2013b), functional disability scores were

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