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"Motoring in idle": The default mode and somatomotor networks are overactive in children and adolescents with functional neurological symptoms

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ABSTRACT

Objective: Children and adolescents with functional neurological symptom disorder (FND) present with diverse neurological symptoms not explained by a disease process. Functional neurological symptoms have been conceptualized as somatoform dissociation, a disruption of the brain's intrinsic organization and reversion to a more primitive level of function. We used EEG to investigate neural function and functional brain organization in children/adolescents with FND.

Method: EEG was recorded in the resting eyes-open condition in 57 patients (aged 8.5–18 years) and 57 age- and sex-matched healthy controls. Using a topographical map, EEG power data were quantified for regions of interest that define the default mode network (DMN), salience network, and somatomotor network. Source localization was examined using low-resolution brain electromagnetic tomography (LORETA). The contributions of chronic pain and arousal as moderators of differences in EEG power were also examined.

Results: Children/adolescents with FND had excessive theta and delta power in electrode clusters corresponding to the DMN—both anteriorly (dorsomedial prefrontal cortex [dmFPC]) and posteriorly (posterior cingulate cortex [PCC], precuneus, and lateral parietal cortex)—and in the premotor/supplementary motor area (SMA) region. There was a trend toward increased theta and delta power in the salience network. LORETA showed activation across all three networks in all power bands and localized neural sources to the dorsal anterior cingulate cortex/dmPFC, mid cingulate cortex, PCC/precuneus, and SMA. Pain and arousal contributed to slow wave power increases in all three networks.

Conclusions: These findings suggest that children and adolescents with FND are characterized by overactivation of intrinsic resting brain networks involved in threat detection, energy regulation, and preparation for action.

1. Introduction

Functional neurological symptom disorder (FND) involves disturbances of body function characterized by neurological sensory or motor symptoms. Patients with FND present with many diverse symptoms not explained by neurological disease, including: psychogenic non-epileptic seizures (PNES); positive movements such as tremor, dystonia, or gait abnormalities; loss of motor functions such as leg or arm paresis; and loss of sensory functions such as blindness, deafness, or loss of feeling in the limbs. Known medical factors do not explain these symptoms or the impairment they confer. In children and adolescents, functional neurological symptoms are generated in the context of pain, injury, intense distress, or psychological trauma, are associated with states of high arousal (Kozlowska et al., 2015a; Kozlowska et al., 2017a;

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Kozlowska et al., 2017b), and are comorbid with medically unexplained pain, nonspecific somatic symptoms, anxiety, and depression (Ani et al., 2013; Kozlowska et al., 2007). Functional neurological symptoms have been conceptualized as somatoform dissociation (Janet, 1889; Janet, 1892/1894; Nijenhuis et al., 1998; Vuilleumier and Cojan, 2011; Barzegaran et al., 2016), which is thought to involve a disruption of the brain's intrinsic organization, and reversion to a more primitive level of neural function (Jackson, 1884)—a brain state where the influence of emotionally salient information on motor output (self-protective reflexive behaviour) is prioritized (Blakemore et al., 2016). Since electroencephalogram (EEG) recordings provide a direct index for quantifying neural function and investigating functional brain organization (Boord et al., 2007; Nagata et al., 1989; Alper et al., 2006), we used EEG to investigate whether functional brain organization is disrupted, at rest, in children and adolescents presenting with acute functional neurological symptoms.

A central idea from evolutionary neuroscience is that functional networks of the brain are organized along a phylogenetic hierarchy that reflects stages in development (Jackson, 1884; MacLean, 1990; Knyazev, 2012; Arnsten, 2015). According to this framework each functional network reflects distinct ways of solving adaptive challenges (Knyazev, 2012; Mesulam, 1998; Buzsaki and Draguhn, 2004; Arnsten, 2015). The particular challenges encountered in any particular situation determine the level of physiological and cortical arousal, the activation state of the brain's innate immune effector cells (glial cells) (Frank et al., 2016), and the functional network that comes into play (Knyazev, 2012; Arnsten, 2015; Hermans et al., 2011; Ding et al., 2013).

States of calm and safety facilitate cognitive/integrative processing, which relies on higher cognitive functions mediated by the prefrontal cortex (PFC), which itself has an executive role in motor planning and motor-control functions—including the inhibition of inappropriate behaviours (Zhang et al., 2012; Knyazev et al., 2017). Such evolutionarily "advanced" processes become operational with maturation and involve activation of cortical brain regions. These processes are associated with the higher-frequency bands (alpha, beta, and gamma) of the EEG (Knyazev, 2007; Knyazev, 2012; Knyazev et al., 2017). By contrast, danger and states of high arousal require emotion and motor-sensory processing; catecholamines impair the higher executive functions of the PFC (Arnsten, 2015; Hermans et al., 2011) and strengthen reflexive control of behaviour (Arnsten, 2015; Hermans et al., 2011). Catecholamines also activate the brain's glial cells, which are more numerous in subcortical versus cortical regions (Mittelbronn et al., 2001), and which function as neuromodulators on a network level, regulating levels of network excitability and resetting basal responsiveness of neural circuits (Ding et al., 2013). Via all these mechanisms, in the face of danger, the brain prioritizes older, more primitive processes—homeostatic defensive functions that include energy regulation, autonomic activity, respiratory rhythms, processing of homeostatic and pain afferents, and activation of innate fear responses and other automatic behaviours—which involve activation of subcortical and limbic structures, and are associated with the low-frequency bands (delta and theta) of the EEG (Knyazev, 2007; Knyazev, 2012).

Evidence from contemporary imaging studies has enabled the identification of the functional networks that are central to the organization of the brain at rest and during task-evoked states (Raichle, 2015; Williams, 2017; Gordon et al., 2016). At rest, the default mode network (DMN), defined by nodes in the medial PFC, posterior cingulate/precuneus cortex, and lateral temporoparietal cortex, is thought to have an important role in self-directed thought and the capacity to switch flexibly into and among alert states (Hagmann et al., 2008; Raichle, 2015). Various mental disorders have already been conceptualized in terms of specific dysfunctions in the DMN (Williams, 2017; Wang et al., 2016), and it is reasonable to assume that disorders of dissociation, including the full spectrum of functional neurological symptoms, will likewise involve disruptions in the DMN.

The DMN is also involved in energy regulation, as is the salience network, the limbic network defined by the anterior insula, dorsal anterior cingulate cortex (ACC), and amygdala (Menon and Uddin, 2010; Williams, 2017). Kleckner et al. (2017) have determined that the default mode and salience networks —operate together as a single, allostatic-interoceptive brain system that maintains energy regulation in the body and that also supports a wide range of psychological functions such as emotion processing, pain processing, memory, and decision making (Kleckner et al., 2017). This allostatic-interoceptive brain system continuously predicts the body's energy needs and uses these predictions to regulate the body's physiological systems to maintain energy regulation in the body (allostasis). In this way, in the face of danger, this system anticipates the body's increased need for energy and activates brain-body systems that enable increased energy consumption. When the danger has passed, the allostatic-interoceptive system changes its predictions and readjusts the energy-regulation system. Activation of the allostatic-interoceptive system is adaptive in the short term but maladaptive in the long term. Continued activation of the system increases the risk for a broad range of stress-related physical and psychological disorders (McEwen and Gianaros, 2011). Accumulating evidence suggests that patients with FND show activation of brain-body systems—the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, and brain systems underpinning arousal—that mediate increases in arousal and energy consumption (Bakvis et al., 2009a; Bakvis et al., 2009b; Kozlowska et al., 2015a; Apazoglou et al., 2017; Voon et al., 2010). These data suggest that maladaptive activation of the allostatic-interoceptive brain system, together with aberrant activation/disruption of motor systems (Blakemore et al., 2016), may be a core feature of FND.

Functional magnetic resonance imaging (fMRI) studies with adult patients with PNES show overactivation and over- and under-connectivity of the intrinsic organization of the brain at rest. In a study using seed regions, van der Kruijs et al. (2012) showed enhanced connectivity between the insula (part of the salience network) and multiple other seed regions: the central sulcus, posterior cingulate cortex, anterior cingulate cortex, and parietal occipital fissure (van der Kruijs et al., 2012). In a later study, using whole-brain analyses, van der Kruijs et al. (2014) showed increased coactivations in resting-state cortical networks as identified by Smith et al. (2009): increased coactivation of the precuneus and (para-)cingulate gyri in the DMN; increased coactivation of the orbitofrontal, insular, and subcallosal cortex in "fronto-parietal network"; increased coactivation of the cingulate and insular cortex in the "executive control network"; increased coactivation of the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri, and supplemental motor cortex in the "sensorimotor network" (van der Kruijs et al., 2014). With the exception of the default mode and sensorimotor networks (also known as the somatomotor network, the term used in the present study), the networks identified by Smith and taken up by van der Kruijs are not always exactly the same as those identified in other studies (Williams, 2017; Menon and Uddin, 2010).

A resting-state study with adult patients with motor symptoms (both positive and negative) also showed over- and under-connectivity of the intrinsic organization of the brain at rest (Wegrzyk et al., 2017). Changes in regions that define the DMN and in subcortical regions mediating motor and affective functions—increased connectivity between the paracentral lobule and frontal regions (bilateral mid orbital gyri), increased connectivity between the subcortical (right caudate) region and both the limbic (left amygdala) and parietal regions (bilateral postcentral gyri), and decreased connectivity between the parietal regions (right temporoparietal region, including the inferior parietal lobule) and frontal regions (right superior orbito-frontal gyrus)—were most helpful in differentiating patients from healthy controls (Wegrzyk et al., 2017).

Resting-state EEG studies in patients with PNES also suggest changes in cortical function: decreased coherence between frontal and