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Disruptions in cortico-subcortical covariance networks associated with anxiety in new-onset childhood epilepsy

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ABSTRACT

Anxiety disorders represent a prevalent psychiatric comorbidity in both adults and children with epilepsy for which the etiology remains controversial. Neurobiological contributions have been suggested, but only limited evidence suggests abnormal brain volumes particularly in children with epilepsy and anxiety. Since the brain develops in an organized fashion, covariance analyses between different brain regions can be investigated as a network and analyzed using graph theory methods. We examined 46 healthy children (HC) and youth with recent onset idiopathic epilepsies with ($n = 24$) and without ($n = 62$) anxiety disorders. Graph theory (GT) analyses based on the covariance between the volumes of 85 cortical/subcortical regions were investigated. Both groups with epilepsy demonstrated less inter-modular relationships in the synchronization of cortical/subcortical volumes compared to controls, with the epilepsy and anxiety group presenting the strongest modular organization. Frontal and occipital regions in non-anxious epilepsy, and areas throughout the brain in children with epilepsy and anxiety, showed the highest centrality compared to controls. Furthermore, most of the nodes correlating to amygdala volumes were subcortical structures, with the exception of the left insula and the right frontal pole, which presented high betweenness centrality (BC); therefore, their influence in the network is not necessarily local but potentially influencing other more distant regions. In conclusion, children with recent onset epilepsy and anxiety demonstrate large scale disruptions in cortical and subcortical brain regions. Network science may not only provide insight into the possible neurobiological correlates of important comorbidities of epilepsy, but also the ways that cortical and subcortical disruption occurs.

1. Introduction

Anxiety disorders represent a prevalent and problematic interictal psychiatric comorbidity in both adults and children with epilepsy (Beyenburg et al., 2005; Caplan et al., 2005; Ekinci et al., 2009; Goldstein and Harden, 2000; Jones, 2014; Kimiskidis and Valeta, 2012; Kwon and Park, 2014; Reilly et al., 2011; Vazquez and Devinsky, 2003). This relationship has been demonstrated through clinic- (Caplan et al., 2005; Brandt et al., 2010; Ettinger et al., 1998; Johnson et al., 2004; Kwon and Park, 2013), community- (Stefanello et al., 2011) and population-based investigations (Gaitatzis et al., 2004; Kobau et al., 2006; McDermott et al., 1995; Reilly et al., 2015; Tellez-Zenteno et al., 2007). Increased anxiety adversely impacts quality of life (QOL) in epilepsy (Johnson et al., 2004; Choi-Kwon et al., 2003; Kwan et al., 2009), explaining more variance in QOL than traditional clinical seizure variables such as seizure control (Johnson et al., 2004).

The cause(s) underlying elevated symptoms of anxiety and anxiety disorders has been controversial. One view is that anxiety disorders are an expected consequence of the onset, course, and treatment of epilepsy including personal fear of seizures and safety as well as potential unpleasant societal reactions that can result in felt stigma (Asadi-Pooya et al., 2007; de Souza and Salgado, 2006; Gandy et al., 2012; Victoroff et al., 1994). Anxiety symptoms may also be elevated in non-affected persons but who have been exposed to family members with epilepsy such as parents and siblings (Baki et al., 2004; Jones and Reilly, 2016), suggesting that stresses associated with epilepsy may even affect those close to the patient, although the possibility of familial aggregation of anxiety disorders must be considered (c.f., Shimada-Sugimoto et al., 2015 for review).

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An alternative view is that anxiety disorders in epilepsy are the consequence of untoward pathophysiological effects of epilepsy on the neural systems that mediate emotional function (Yilmazer-Hanke et al., 2015), a classic example being the relationship between ictally elicited fear states in epilepsy and the amygdala (Cendes et al., 1994; Guimond et al., 2008). Furthermore, both atrophy and hypertrophy of the amygdalae have been reported in adults with epilepsy (Cendes et al., 1994; Minami et al., 2015) and linked to interictal psychopathology (Tebartz van Elst et al., 1999). Increased amygdala volume has also been reported in children with chronic focal (Daley et al., 2008) and generalized epilepsy (Schreibman Cohen et al., 2009) and associated with anxiety disorders and depression.

Also supporting a neurobiological view are findings that behavioral problems in general and anxiety disorders in particular can be detected not only very early in the course of uncomplicated pediatric epilepsies, but may be present antecedent to the first recognized seizure and epilepsy diagnosis (Austin et al., 2001; Jones et al., 2007). Furthermore, recent findings indicate that children with new-onset epilepsy and anxiety disorders exhibit enlarged amygdala (left) and reduced thickness of the left medial orbitofrontal, right frontal pole, and right lateral orbitofrontal regions (Jones et al., 2015), suggesting disrupted circuitry in networks known to mediate anxiety.

While provocative, to date only a very limited, albeit hypothesis-driven set of neural regions have been examined in regard to their association with anxiety disorders. A larger issue is the degree to which diffuse cortical and subcortical networks may be differentially affected in children with epilepsy with anxiety disorders compared to non-anxious children with epilepsy and HC, and here network science may be especially informative in characterizing the complex systems involved (Mears and Pollard, 2016). GT is a mathematical approach to understanding systems as networks. Given that cortical and subcortical structures develop in an organized fashion, covariance analyses between different brain regions can be investigated as a network and analyzed using GT methods, a methodology increasingly used in functional connectivity analyses, white matter connectivity, and covariance analyses of cortical and subcortical volumes in both healthy and medical illness populations (Balardin et al., 2015; Ma et al., 2016; Yeo et al., 2016) including epilepsy (Bernhardt et al., 2016; Gleichgerrcht et al., 2015; Song et al., 2015).

It has been increasingly recognized that brain maturation in childhood involves an organizational process that optimizes network efficiency (Bullmore and Sporns, 2012). The strengthening of network coherence with enhanced cortical thickness covariance in childhood is particularly evident in association cortices compared to primary cortices (e.g. motor, sensorimotor and visual areas), suggesting the orchestration of a more efficient inter-cortical information transfer (Lerch et al., 2006). Epilepsy appears to disrupt this large-scale topology. In children with recent-onset idiopathic epilepsies, cortical volumes covariance was altered with higher network segregation and reduced global integration compared with controls, suggesting alteration of large-scale brain networks. Further, this configuration was more vulnerable to simulated network targeted attacks, implying that this altered network might have fewer parallel or alternative pathways to maintain global integrity (Bonilha et al., 2014). Adults with temporal lobe epilepsy (TLE) also exhibit less network efficiency compared to controls (increased path length and clustering, altered distribution of network hubs) (Bernhardt et al., 2011). It is assumed that anxiety disorder will further compromise brain network configurations in epilepsy. Evidence for this network alteration has only been indirectly inferred from the psychiatric literature. However, there is no direct evidence that anxiety disorder impairs network function in childhood onset epilepsy beyond alterations expected in epilepsy without anxiety.

In this investigation we examined typically developing children as well as youth with recent idiopathic epilepsies with and without anxiety disorders. Network analysis using GT investigated the covariance of diverse cortical and subcortical regions to determine whether and in what way children with epilepsy and anxiety disorders differed compared to non-anxious children with epilepsy and HC. Specifically, we examined the global properties of their networks, the most central/important regions in the configuration of the networks, and the hubs or those areas facilitating communication between pairs of regions. Furthermore, we investigated the network of regions demonstrating high synchronization to amygdala enlargement in the group of children with epilepsy and anxiety in order to determine the influence of those amygdala abnormalities on other neural systems.

2. Materials and methods

2.1. Participants

Study participants included 86 children with recent-onset idiopathic epilepsies and 48 HC aged 8–18 years (Table 1). Inclusion criteria were a diagnosis of epilepsy within the past 12 months, no other developmental disabilities or neurological disorders, normal neurologic examinations, and normal clinical imaging results. A board certified pediatric neurologist (blinded to interview data) confirmed that all participants had focal (idiopathic localization-related epilepsy–ILRE) or generalized (idiopathic generalized epilepsy–IGE) seizures and provided independent confirmation of specific epilepsy syndromes. Participants with focal epilepsies were comprised of children with rolandic epilepsy (22.1%), temporal lobe epilepsy (TLE) (8.1%), frontal epilepsy (9.3%), childhood occipital epilepsy (COE) (1%), and focal epilepsy NOS (10.5%). Participants with generalized epilepsies include juvenile myoclonic epilepsy (JME) (30.2%), absence epilepsy (14.0%), and generalized epilepsy NOS (4.7%).

HC were age-matched first-degree cousins of epilepsy participants who presented no history of seizures, current anxiety disorder, any initial precipitating injuries (e.g., febrile convulsions), other developmental or neurologic disease, or loss of consciousness >5 min. First-degree cousins were used as controls rather than siblings for the following reasons: (i) first-degree cousins are more genetically distant from the participants with epilepsy and thus less predisposed than siblings to shared genetic factors that may contribute to anomalies in brain structure and cognition; (ii) a greater number of first-degree cousins are available than siblings in the target age range; and (iii) the family link was anticipated to facilitate participant recruitment and retention over time. All children and parents participated in a psychiatric diagnostic interview and underwent magnetic resonance imaging (MRI). Further information about participants and the inclusion and exclusion criteria can be found in previous publications (Hermann and Jones, 2006).

2.2. Psychiatric diagnostic interview

Every participant and their parents separately participated in a semi-structured interview using the Kiddie–Schedule for Affective Disorders

Table 1
Demographic and clinical characteristics of participants.

	Healthy controls ($n = 48$)	Epilepsy non-anxious ($n = 62$)	Epilepsy and anxiety ($n = 24$)
Age (mean ± SD)	13.30 ± 3.17	12.85 ± 3.50	12.05 ± 2.93
Sex (male/female)	21/27	33/29	9/15
Education	7.02 ± 3.03	6.83 ± 3.65	5.87 ± 2.85
IQ* (mean ± SD)	108.8 ± 10.6	102.1 ± 15.2	101.7 ± 15.6
Syndrome onset (months: mean ± SD)	–	6.63 ± 3.65	7.26 ± 3.89
AED (yes/no)	–	54/8	17/7
Epilepsy syndrome (ILRE/IGE)	–	28/34	16/8

* Significant between groups at a $p < 0.05$. Education represents years of school attendance.