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Resting state functional network disruptions in a kainic acid model of temporal lobe epilepsy

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ABSTRACT

We studied the graph topological properties of brain networks derived from resting-state functional magnetic resonance imaging in a kainic acid induced model of temporal lobe epilepsy (TLE) in rats. Functional connectivity was determined by temporal correlation of the resting-state Blood Oxygen Level Dependent (BOLD) signals between two brain regions during 1.5% and 2% isoflurane, and analyzed as networks in epileptic and control rats. Graph theoretical analysis revealed a significant increase in functional connectivity between brain areas in epileptic than control rats, and the connected brain areas could be categorized as a limbic network and a default mode network (DMN). The limbic network includes the hippocampus, amygdala, piriform cortex, nucleus accumbens, and mediodorsal thalamus, whereas DMN involves the medial prefrontal cortex, anterior and posterior cingulate cortex, auditory and temporal association cortex, and posterior parietal cortex. The TLE model manifested a higher clustering coefficient, increased global and local efficiency, and increased small-worldness as compared to controls, despite having a similar characteristic path length. These results suggest extensive disruptions in the functional brain networks, which may be the basis of altered cognitive, emotional and psychiatric symptoms in TLE.

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1. Introduction

1.1. Temporal lobe epilepsy and networks

Temporal lobe epilepsy (TLE) is a common type of focal epilepsy. It is characterized by spontaneously recurring focal dyscognitive seizures that originate from the temporal lobe, often from mesial structures such as the hippocampus and amygdala. In about one-third of the patients with TLE, it is debilitating because it is difficult to control by antiepileptic drugs (AEDs), and often associated with behavioural, cognitive and psychiatric disturbances in the interval between seizures (i.e. interictal period) or immediately after the seizures (i.e. postictal period).

The interictal behavioural and cognitive disturbances in TLE suggest that large areas of the brain are affected. A temporal lobe seizure may spread to many brain areas directly and indirectly connected to the temporal lobe, which include limbic and frontal brain structures (Bartolomei et al., 2004; Bertram et al., 1998). These findings suggest a deleterious impact of TLE on the whole brain, potentially impacting multiple brain networks (Laufs, 2012; Morgan et al., 2011; Tracy et al., 2014).

1.2. Resting state networks and graph theoretical networks

In functional magnetic resonance imaging (fMRI), the correlations between spontaneous low-frequency fluctuations of a Blood Oxygen Level Dependent (BOLD) signal provide a measure of the functional connectivity in normal and pathological condition. A prominent resting state network (RSN) in normal subjects is the default mode network (DMN) involving the medial prefrontal cortex, medial temporal lobe and cingulate cortex (Gozzi and Schwarz, 2016; Greicius et al., 2009). DMN appears to be homologous across humans, monkeys, and rodents (Lu et al., 2012; Sierakowiak et al., 2015). The DMN is most active at rest (awake with eyes closed), and persists in moderate anaesthesia (Hutchison et al., 2014; Wang et al., 2011). DMN disruptions and disconnection with other parts of the brain have been reported during the interictal state in TLE patients (Laufs et al., 2007; Liao et al., 2010).

Topological properties of a brain network can be analyzed by graph theoretical analysis (Bullmore and Sporns, 2009), by representing brain regions as nodes and structural/functional connection pathways as

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edges. In a graph theoretical framework, functional networks can be objectively characterized by different mathematical measures (see Rubinov and Sporns, 2010, for a non-technical review). Watts and Strogatz (1998) defined small-world networks as a class of networks with significantly more clustering than random networks, while still having a similar characteristic path length as random networks. Networks in the brain are hypothesized to optimize local processing and global integration (Meador, 2011; Stam and Reijneveld, 2007b). In TLE patients, controlling abnormal networks can play a substantial role in guiding targeted interventions and therapies (Lopes da Silva et al., 2012).

A host of studies investigating structural and functional interictal brain networks in TLE patients and control subjects, using EEG, MEG and MRI, have yielded mixed and ambiguous results (see Bernhardt et al., 2015, for review). Irreconcilable bidirectional changes in both the network connectivity and the graph theoretical measures have been reported. For instance, using fMRI data, Liao et al. (2010) reported reduced clustering coefficients and path lengths along with an increased connectivity within the medial temporal lobe and decreased connectivity within the DMN. Vaessen et al. (2012) reported reduced clustering but increased path lengths in TLE patients with cognitive decline, while Chiang and Haneef (2014a) reported increase in clustering and path lengths. Increase in clustering and path lengths in TLE patients was also found using structural MRI data (Bernhardt et al., 2011) or EEG data (Horstmann et al., 2010). Thus, while TLE patients appear to exhibit disruptions of both local segregation and global integration, the actual change remains unequivocal.

The inconsistent results on TLE patients could result from heterogeneity of the patient population. In addition, because of preexisting genetic factors and patient-selective history, it is unclear whether the disruptions of RSNs in human TLE are caused by seizure activity only. In addition, ethical concerns prevent experimental studies in humans, although these studies are necessary to elucidate the underlying mechanisms. Thus, we used an animal model of TLE in an attempt to study the RSN disruptions in human TLE.

1.2.1. Study of resting state networks in an animal model of TLE

The TLE model selected was kainic acid induced status epilepticus (SE) in rats. Systemic administration of kainic acid in rats leads to prolonged limbic seizures lasting for several hours, and with increasing severity indicated by wet-dog shakes, facial and forelimb clonus, and then rearing, falling and jumping (Dudek and Edward, 2005). Following a seizure-free latent period of 2–3 weeks, kainate-treated epileptic rats manifested spontaneous recurrent seizures throughout their lifespan (Sperk et al., 1985). The behavioural, electroencephalographic, and neuropathological features of the kainate-induced model resemble those of human TLE (Buckmaster, 2004; Dudek and Edward, 2005; Lévesque and Avoli, 2013).

The present study focuses on characterizing alterations in the resting-state networks of kainate-treated epileptic rats. This follows our original report of multiple RSNs in anaesthetized rats (Hutchison et al., 2010). To our knowledge, RSNs have not been studied in animal models of TLE. In a tetanus toxin induced rat model of neocortical focal epilepsy, Otte et al. (2012) demonstrated an increase in clustering and path length.

The objective of this study was to elucidate the changes in functional connectivity between various regions of the brain in a model of TLE in rats, by recording fMRI BOLD signals in kainate-treated epileptic rats and age-matched, saline-treated controls. We hypothesized that both the local and global functional connectivity will be significantly altered in this rodent model of TLE, as analyzed by a graph theoretical approach.

2. Materials & methods

2.1. Animals

Adult male Long-Evans rats (Charles River, St. Constance, Quebec, Canada) weighing 250–400 g were used in these experiments. Rats were housed in standard cages and subjected to 12:12 h light (7–19 h)/dark cycle. Food and water was accessible ad libitum, in a temperature regulated environment. The study was conducted in accordance with the guidelines established by the Canadian Council on Animal Care and approved by the local Animal Use Subcommittee. All experiments were conducted during the light phase (8–19 h).

2.2. Induction of spontaneous seizures using kainic acid

Kainic acid (Abcam Biochemicals, Cambridge, MA) was administered intraperitoneally (i.p.), using an incremental dose protocol modified from (Dudek and Edward, 2005), to induce SE in rats. Adult male rats were randomly allocated to either sham saline treatment ($n = 11$; initial weight 255 ± 5.8 g, mean ± standard error of the mean (SEM)) or kainic acid treatment, of which 8 rats with spontaneous seizures were used for fMRI connectivity study (initial weight: 247 ± 3.9 g, $n = 8$; not different from saline group). In the kainate group, rats were injected with an initial dose of 5 mg/kg i.p. kainic acid (diluted to 10 mg/mL with sterile saline), and monitored for behavioural seizures stages according to Racine (1972) [stage 3, forelimb clonus; stage 4, rearing with forelimb clonus; stage 5, rearing and falling with forelimb clonus]. If convulsive (>stage 3) seizure did not occur, a subsequent half dose of 2.5 mg/kg was administered at ~1 h after the initial dose. Incremental repeated doses (2.5–5.0 mg/kg) were administered to the rats until they developed stage 5 seizures or exhibited convulsive (stage 3 to 5) seizures for >3 h. Age matched controls were injected with a similar volume of sterile saline (0.1–0.2 mL i.p.) as kainic acid injected rats. Diazepam (Sandoz, Canada; 5 mg/mL) was administered (4 mg/kg i.p.) to stop the seizures after 3 h of stage 5 seizure. Sterile saline (1.5–2.5 mL, 2×) was administered subcutaneously to hydrate the rats; shortly after diazepam. Starting 2–3 weeks following seizure induction, kainate-treated rats were monitored for signs of behavioural seizure activity, for 1–2 h every other day, with at least one overnight video monitoring at 3 weeks. Only animals that showed 2 or more spontaneous seizures over a period of 2 to 3 weeks were used for scanning.

2.3. Functional magnetic resonance imaging procedures

2.3.1. Animal usage and preparation

The first scan was taken 4–5 weeks after the kainate/saline-treatment. The occasional rats that showed behavioural seizure activity on the day of the scan were excluded. General anaesthesia in rats was induced with 5% isoflurane in oxygen flowing at 1.5 L/min from a calibrated vapourizer (Harvard Apparatus, Holliston, MA). Once under anaesthesia, 2% isoflurane was delivered via a custom nose-cone (serving partially as a bite bar), and the rat was secured to a custom-built nylon stereotaxic frame with ear bars (Mirsattari et al., 2005), with the frame sitting on a cradle that was later inserted into the bore of the scanner. Respiration was spontaneous throughout the experiment, and was monitored by a pneumatic pillow (SA Instruments, Stony Brook, NY) wrapped around the rat's chest wall. The rat's body temperature was maintained at 37 °C via a feedback-controlled system, using a rectal fiber-optic probe (SA Instruments) and a water-circulated heating pad (TP500, Gaymar Industries, Orchard Park, NY). Heart rate and blood oxygen saturation level were measured using a pulse oximeter (MR-compatible; 8600 V, Nonin Medical, Plymouth, MN) positioned on the hind-paw. Physiological parameters were in the normal range (temperature: 37 ± 0.5 °C, heart rate: 250–390 beats/min, breathing rate: 60–90 breaths/min, oxygen saturation: >95%) for the entire recording/scanning session.

2.3.2. Image acquisition

A minimum of 30 min was allowed for equilibration at 2% isoflurane, during which shimming and image localization were performed. Then the rats were scanned for approximately 60 min at 4 end-tidal isoflurane concentrations in the order of 2.0%, 1.5%, 1.0%, and 0.5%

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