Gamma-Band Neural Synchronization is Associated with Motor Difficulties in Childhood Epilepsy

by

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A thesis submitted in conformity with the requirements for the degree of Master of Arts
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Abstract

The present study used magnetoencephalographic (MEG) recordings during median nerve stimulation in children with epilepsy to investigate the hypothesis that abnormal inter-regional gamma-band synchronization within the sensorimotor network is related to motor performance difficulties. Stimulation-dependent gamma-band network synchronization following median nerve stimulation was identified by network based statistics (NBS) and involved the primary motor and somatosensory cortex. Lateralization of the synchronization network contralateral to the stimulated arm was observed and this lateralization was also found in the graph properties of strength, clustering and centrality of primary motor and somatosensory cortex. Significant associations between graph properties of primary motor and somatosensory cortex, reflecting the participation of these regions in the stimulation-dependent network, and motor performance in grooved pegboard and finger tapping tests for the contralateral hand were observed. These findings are congruent with the view that epilepsy may lead to performance deficits through the disruption of connectivity in functional brain networks.
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Chapter 1
Introduction

1 Neural Oscillations and Synchronization and Their Relationship with Brain Functions and Development

Neural oscillations refer to periodic variations of excitability in groups of neurons (Buzsáki & Watson, 2012; Schnitzler & Gross, 2005). Produced by dynamical interaction between cellular and synaptic mechanisms, neural oscillations represent a general feature of neural firing patterns (Wang, 2003). Neural communication reflected by neural oscillations serves as a very important mechanism underlying human brain functions (Buzsáki & Watson, 2012). Neural oscillations have been found to be related to a variety of brain functions such as the coordination of activity and information among brain regions (Buzsáki & Watson, 2012). These activities support efficient human brain information processing underlying a variety of cognitive and motor functions: For example, neural oscillations in theta and gamma bands were found closely associated with human memory processes, and neural oscillations in alpha and gamma bands were found related to attention (Ward, 2003). Neural oscillations within motor cortex were found related to movement preparation during voluntary movement (Sanes & Donoghue, 1993). Neural oscillations in 6-9 Hz within the cerebello-thalamo-cortical loop are associated with people’s slow finger movements, possibly underlying the mechanism of ‘intermittent control of continuous movement’ (Groß et al., 2002, p. 2299).

Moreover, neural oscillations in gamma band, in particular, were found to be especially important in providing temporal structure for information processing in the brain (Bartos, Vida, & Jonas, 2007), and critical in neural communication and synaptic plasticity (Jensen, Kaiser, & Lachaux, 2007). Neural oscillations in gamma band were found to be closely associated with various human attention and memory functions (Jensen, Kaiser, & Lachaux, 2007). Gamma-band neural oscillations within motor cortex have also been found to be related to changes of
behavioral condition during voluntary movement (Donoghue, Sanes, Hatsopoulos, & Gaál, 1998).

Synchronization of neural oscillations reflects the temporally precise interactions between neural activities, mediated by pairs of action potentials within a particular oscillation cycle (Schnitzler & Gross, 2005). Conscious awareness was proposed to arise from neural oscillatory synchronization throughout the brain (Ward, 2003). Neural oscillatory synchronization is also fundamental to a variety of brain functions, including both cognitive and motor abilities (Schnitzler & Gross, 2005): For example, long-range neural oscillatory synchronization within the fronto-parieto-temporal attentional network in beta band is related to attention demands and behavioral performance in visual attention tasks (Gross et al., 2004). Large-scale theta-band neural synchronization between bilateral frontal regions and between the left frontal and right temporal–parietal regions are involved in verbal and spatial working memory binding (Wu, Chen, Li, Han & Zhang, 2007). Beta-band neural synchronization between frontal and posterior temporal-parietal area in both hemispheres related to gap-filling in online sentence processing which requires high semantic working memory load (Haarmann, Cameron, & Ruchkin, 2002). Moreover, neural oscillatory synchronization was suggested to serve to as a sensorimotor mechanism for gathering and interacting information to guide motor actions (MacKay, 1997). Beta-band neural synchronization within the basal ganglia was suggested to be related to action preparation (Jenkinson & Brown, 2011). Synchronized neural activities within primary motor cortex of monkeys have been observed during precision grip tasks and may serve as a consistent task-dependent modulation (Baker, Olivier, & Lemon, 1997; Baker, Kilner, Pinches, & Lemon, 1999; Baker, Spinks, Jackson, & Lemon, 2001).

Gamma-band neural oscillatory synchronization, in particular, serves as a binding mechanism underlying the brain’s perceptual, cognitive and motor functions (Ribary, 2005; Schnitzler & Gross, 2005). Gamma-band neural oscillatory synchronization serves to bind the processing in different brain regions and to establish a coherent concept (Tallon-Baudry & Bertrand, 1999). Gamma-band neural synchronization is related to a variety of cognitive and motor functions, such as sensory-motor integration, top-down modulation of sensory processes, attention, arousal, object recognition and working memory (Singer, 1999; Engel, Fries, & Singer, 2001;
Engel & Singer, 2001; Ward, 2003; Uhlaas & Singer, 2006; Fries, 2009). For example, gamma-band neural synchronization within orbitofrontal cortex reflected inhibitory control over a subgroup of neurons conveying information about emotion valence relating to motor decisions (van Wingerden, Vinck, Lankelma, & Pennartz, 2010).

Neural synchronization was found to be related to brain development. Uhlhass and colleagues (2009) used Gestalt perception tasks found that increased neural synchrony was related to cognitive performance until early adolescence; Decreased neural synchrony in late adolescence was found and it was related to reduced task performance, followed by a reorganization of gamma-band and beta-band synchrony after this period (Uhlaas et al., 2009). Particularly, gamma-band neural oscillatory synchronization was also found closely relevant for the development of cortical circuits (Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). Gamma-band neural synchronization was proved to be critical in children’s cognitive and linguistic development (Benasich, Gou, Choudhury, & Harris, 2008).

2 Neural Synchronization Is Relevant for Numerous Neurological and Psychiatric Disorders, Including Childhood Disorders

Neural oscillation patterns were found to be remarkably stable within individuals (Gasser, Bächer, & Steinberg, 1985), and to have higher similarity between monozygotic twins than heterozygotic twins and non-twin siblings (Van Beijsterveldt, Molenaar, De Geus, & Boomsma, 1996), suggesting that neural oscillations may be under genetic control, and could be viewed as a robust and quantifiable phenotype (Linkenkaer-Hansen et al., 2007; Buzsáki & Waston, 2012).

Neural oscillations and synchronization can be easily influenced by motor and cognitive activities within a small scale of time (Buzsáki & Brendon, 2012), and many previous studies

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1 Gestalt perception tasks required integrating separate elements into coherent object representation (Uhlaas et al., 2006).
have focused on the role of measureable signals of neural oscillations and synchronization in various neurological and psychiatric disorders. Abnormal neural oscillations and synchronization has been found associated with a variety of neural and psychiatric disorders, including epilepsy, schizophrenia, autism, dementia, Alzheimer's disease and Parkinson’s disease (Schnitzler & Gross, 2005; Uhlhaas & Singer, 2006; Uhlhaas, Haenschel, Nikolić, & Singer, 2008; Buzsáki & Waston, 2012).

For example, alterations in oscillations and synchronization within the basal ganglia and between subcortical and cortical structures were found to be fundamental to pathophysiology of Parkinson’s diseases (Schnitzler & Gross, 2005; Gatev, Darbin, &Wichmann, 2006). Increased resting-state cortico-cortical functional connectivity in alpha band was found in early stage of Parkinson’s disease (Stoffers et al., 2008). Abnormal neural oscillations within the basal ganglia resulted from functional disruption in the cortical-striatal-thalamo-cortical circuits are associated with pathophysiology of co-occurring Tourette syndrome (Sukhodolsky, Leckman, Rothenberger, &Scahill, 2007). Increased alpha-band and beta-band neural oscillation power and asymmetric alpha-band power in the frontal regions were observed in depression patients (Alhaj, Wisniewski, & McAllister-Williams, 2011; Iositescu, 2011). A decrease of gamma-band neural oscillations in the frontal regions was found in both bipolar disorder and major depressive disorder patients (Lee, Chen, Hsieh, Su, & Chen, 2010). Beta-band and gamma-band neural synchronization was found abnormal in patients with schizophrenia (Uhlaas & Singer, 2010). High thalamocortical coherence in theta band was found in neurogenic pain patients (Sarnthein & Jeanmonod, 2008). Locally increased theta-band coherence within left frontal and temporal regions and globally decreased lower alpha-band coherence was observed in autism spectrum disorders (ASD) patients (Murias, Webb, Greenson, & Dawson, 2007). Neural oscillatory synchronization involving primary motor was found during essential tremor (ET) in some motor disorders (Schnitzler, Münks, Butz, Timmermann, & Gross, 2009). Synchronization network involving both primary motor and somatosensory cortex, as well as supplementary motor area and posterior parietal cortex was found during postural tremor in patients with Wilson’s disease was observed (Südmeyer et al., 2006).
Moreover, neural oscillations and synchronization were also related to a variety of particular cognitive and motor functions in patients of neural and psychiatric disorders. For example, neural oscillations in beta band within basal ganglia interfere with movement execution abilities in patients with Parkinson’s disease, leading to akinesia (Schnitzler & Gross, 2005). In patients with Alzheimer’s disease, decreased beta-band neural synchronization was associated with their cognitive impairments (Stam, van der Made, Pijnenburg, & Schelletnes, 2003). Abnormal neural oscillatory activities were found during the perceptual binding tasks (binding spatially separate perceptual features into a whole) in the patients with autism and Williams Syndrome (Grice et al, 2010). A decrease of neural synchronization both within fusiform face area (FFA) and between FFA and other distant cortical regions was found during viewing faces in patients with ASD (Khan et al., 2013). Reduced beta-band neural synchronization was associated with deficits in Gestalt perception tasks of the schizophrenia patients (Uhlaas et al., 2006).

Abnormal neural oscillatory synchronization has also been observed in children with various neurological and psychiatric disorders, or associated with particular functions of children with disorders. For example, weaker interhemispheric neural synchronization in putative language regions were found in toddlers with autism, indicating disrupted neural synchronization was an important feature in autism neurophysiology in very early stages (Dinstein et al., 2011). The strength of neural synchronization is positively correlated with verbal capabilities of toddlers of autism (Dinstein et al., 2011). Functional disconnection between frontal and visual cortex were found during cross-modal attention tasks in children with attention-deficits/hyperactivity disorder (ADHD) (Mazaheri et al., 2010). Reduced theta-band inter-regional connectivity during set-shifting task was observed in children with ASD (Doesburg, Vidal, & Margot, 2013).

3 Neural Synchronization in Adult and Childhood Epilepsy

Epilepsy (including childhood epilepsy) is associated with a number of cognitive and motor impairments. The neurophysiological basis of these difficulties remains poorly understood.
Previous evidence indicated abnormal neural synchronization in patients, including children, with various types of epilepsy.

For example, disrupted neural synchronization has been found associated with seizures of epilepsy. Inter-neural synchrony was found as a defining aspect of the occurrence of seizures and plays a fundamental role in a variety of impairments in epilepsy (Lemieux, Daunizeau, & Walker, 2011). Abnormal neural oscillations within thalamocortical circuitry may be associated with generalized absence seizures (Snead, 1995). Disrupted neural synchronization between the orbito-frontal cortex and amygdala was found in the patients during focal epileptic seizures (Bartolomei et al., 2005). A decorrelation of multichannel intracranial electroencephalograph (EEG) activity was found during the first half of seizures in focal epilepsy patients (Schindler, Leung, Elger, & Lehnertz, 2007). Increased neural synchronization within thalamo-cortical systems was correlated with the degree of loss of consciousness (LOC) in temporal lobe seizures (Arthuis et al., 2009).

Furthermore, abnormal neural synchronization has been concentrated within epileptogenic brain areas (Ortega, Menendez, Sola, & Pastor, 2008; Warren et al., 2010). In particular, theta-band connectivity alterations were found as a hallmark of tumor-related epilepsy in brain tumor patients (Douw et al., 2010). Excessive high frequency neural oscillations (> 80 Hz) were also known as a biomarker of epileptogenic brain regions (Ochi et al., 2007; Jacobs et al., 2008). High-frequency oscillations in 250-500 Hz (fast ripples) were observed in the regions of seizure initiation in epilepsy (Staba, Wilson, Bragin, Fried, & Engel, 2002; Crépon et al., 2010), and were supposed to reflect localized pathological events about epileptogenesis (Bragin et al., 2002). The interictal high-rate fast ripples were also proposed to be a surrogate marker of the epileptogenic zone (Akiyama et al., 2011). Lower local field potentials (LFP) synchrony between seizure-generating brain regions and other brain regions was found in patients with medically resistant partial epilepsy (Warren et al., 2010). Synchronized intraoperative electrocorticography (EcoG) activity was found at some specific areas of the lateral temporal cortex in drug-resistant temporal lobe epilepsy patients (Ortega, Menendez de la Prida, Sola, & Pastor, 2008).
Some previous research also indicated abnormal neural synchronization within particular functional network in patients of epilepsy. Mesial temporal lobe epilepsy (mTLE) patients were found having decreased functional connectivity within the auditory and sensorimotor network and increased functional connectivity in the primary visual cortex but decreased functional connectivity in the bilateral motion-selective (MT+) regions within the visual network (Zhang et al., 2009a). Moreover, mTLE patients also showed decreased functional connectivity compared with controls within the dorsal attention network (DAN) and the degree of the functional connectivity change was negatively correlated with their Trail Making Test\(^2\) performance (Zhang et al., 2009b), indicating disrupted connectivity in functional brain networks in epilepsy may lead to performance deficits.

Abnormal neural synchronization was also found in childhood epilepsy: Impaired intrinsic connectivity network development was found in children with medically intractable localization-related epilepsy (Ibrahim et al., 2014). High-frequency oscillations (HFO) have been found in children with intractable extrahippocampal localization-related epilepsy during ictal periods (Ochi et al., 2007).

Some studies especially also indicated the association between disrupted neural synchrony and impaired performance deficits in childhood epilepsy: Inter-regional gamma-band desynchronization has been found involving primary motor cortex during seizures in childhood focal epilepsy (focal cortical dysplasia, FCD), which is associated with motor impairments (Ibrahim et al., 2012). Excessive magnetoencephalography (MEG) gamma-band amplitude within primary motor cortex following median nerve stimulation in children with FCD is also associated with motor difficulties (Doesburg et al., 2013). These findings suggested that the alteration of gamma activity and synchrony within the sensorimotor cortex may contribute to motor impairments in childhood epilepsy.

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\(^{2}\)The Trail Making Test (TMT) requires visual search, scanning, speed of processing, mental flexibility, and executive functions (Tombaugh, 2004).
4 Neural Activity and Synchronization within Sensorimotor Cortex and Its Association with Epilepsy

Previous studies in childhood epilepsy have found alterations of gamma activity and synchrony involving sensorimotor cortex which were related to motor difficulties of this group of patients. Sensorimotor cortex involves somatosensory and motor areas in brain (such as precentral and postcentral gyrus, namely primary motor and somatosensory cortex). Sensorimotor cortex involved a variety of oscillatory activities which could be strongly modulated by movement and somatosensory input, especially oscillatory activities in gamma band. Moreover, MEG with ‘spatial filtering source reconstruction methods’ was proposed as an ideal non-invasive method to investigate sensorimotor oscillations and synchronization during various motor tasks (Cheyne, 2013, p. 27). Increased gamma-band neural synchronization was found in sensorimotor cortex during visuomotor tasks (Aoki, Fetz, Shupe, Lettich, & Ojemann, 1999).

The topography of gamma-band event-related synchronization was also proved helpful to provide functional mapping of sensorimotor cortex (Crone, Miglioretti, Gordon, & Lesser, 1998). Moreover, sensorimotor dysfunction, as well as supplementary motor area dysfunction, is related to motor impairments in some neurological and psychiatric disorders (Schröder, Wenz, Schad, Baudendistel, & Knopp, 1995). For example, pathological neural oscillatory synchronization involving primary motor cortex, secondary somatosensory cortex and supplementary motor area was found in patients with Parkinson’s disease (Schnitzler, Timmermann, & Gross, 2006).

Neural activity and oscillations within sensorimotor cortex has also been found associated with the pathophysiology of epilepsy. Epileptic activity in the brain may have a remote effect on the motor cortex inducing abnormal inhibitory circuits (Werhahn, Lieber, Classen, & Noachtar, 2000). Hyperconnectivity between the primary motor cortex and supplementary motor area was found with increasing cognitive demand in patients with juvenile myoclonic epilepsy (Vollmar et al., 2011). Previous research also reported that biofeedback training of sensorimotor cortex oscillations could induce suppression of seizures in epilepsy (Sterman, & Friar, 1972). Small
movements during seizures were found to be related to high frequency gamma-band activity within sensorimotor cortex (Cheyne, 2013).

Previous MEG studies have reported that high frequency response from primary sensorimotor cortex can be activated by median nerve stimulation (Korvenoja et al., 1995; Oishi, 2003). Median nerve stimulation was found associated with neural oscillations within primary and secondary somatosensory cortex (Della Penna et al., 2004). It was known to elicit somatosensory evoked magnetic fields (SEF) which could be measured with MEG (Kawamura et al., 1996), and could be used to analyze sensorimotor integration in some movement disorders (Abbruzzese, Marchese, Buccolieri, Gasparetto, & Trompetto, 2001; Abbruzzese & Berardelli, 2003). Median nerve SEF from primary sensorimotor cortex was also reported to be used to detect abnormal interhemisphere asymmetries of source locations (Wikström et al., 1997). Brain responses produced from median nerve stimulation were observed to be lateralized indicating a dominant role of the contralateral hemisphere in somatosensory information processing (Nikouline et al., 2000).

Previous research related gamma-band activity amplitude within primary motor cortex following median nerve stimulation in children with epilepsy with motor difficulties (Doesburg et al., 2013). No previous research, however, investigated gamma-band neural synchronization following median nerve stimulation in children with epilepsy and its association with motor impairments. The present study thus proposes to use MEG recordings during median nerve stimulation in children with epilepsy to investigate the hypothesis that altered inter-regional gamma band synchronization within the sensorimotor network are related to motor performance difficulties of the patients.

5 Motor Difficulties in Childhood Epilepsy and Related Neuropsychological Evaluation

Childhood epilepsy is associated with a variety of motor impairments. For example, impairments of motor coordination and planning were found in children with frontal lobe
dysfunction (Hernandez, et al., 2002; Patrikelis, Angelakis, & Gatzonis, 2009), and impaired complex motor control was found in children with absence epilepsy (Conant, Wilfong, Inglese, & Schwarte, 2010).

Neuropsychological tests provide useful information about motor impairments of patients with epilepsy (Helmstaedter, 2004; Patrikelis, Angelakis, & Gatzonis, 2009). For example, research using the Purdue Pegboard Test, which examined children’s capability of planning and executing complicated sequential motor acts, has found selective impaired motor coordination functions in children with frontal lobe epilepsy (Riva et al., 2005). Research examining psychomotor speed using the finger tapping test has found poorer performance in children with frontal lobe epilepsy (Braakman et al., 2012). Finger tapping performance of patients with frontal lobe epilepsy has also been found to be correlated to their ages at seizure onset (Upton, & Thompson, 1997).

The present study aims to use three neuropsychological tests to examine motor abilities in a group of children with epilepsy: the grooved pegboard test, finger tapping test and grip strength test (dynamometer test). The grooved pegboard test was used to examine the participants’ fine motor dexterity and speed (Strauss, 2006). The finger tapping test was used to examine the participants’ motor speed (Schatz, 2011). The grip strength or dynamometer test was used to examine the participants’ handgrip strength.

6 Approaches of Analyzing Neural Synchronization: Graph Theory Analysis and Network Based Statistics

Graph theory has been largely used in the quantitative analysis of brain’s structural and functional networks. In particular, a graph refers to a set of connected nodes in a complex network\(^3\) (Bullmore & Sporns, 2009). Viewing the brain as a complex network of interactive

\(^3\) A complex networks refer to a network with certain topological features (Bullmore & Sporns, 2009).
dynamical systems’ provided new approaches and insights into analyzing higher level brain functions and pathophysiology (Reijneveld, Ponten, Berendse, & Stam, 2007). Graph theory analysis was broadly used to analyze neural network synchronization in a variety of neurological and psychiatric disorders, such as epilepsy, brain tumors, Alzheimer’s disease, schizophrenia and so on (Bartolomei et al., 2006; Stam & Reijneveld, 2007; de Haan et al., 2009; Stam et al., 2009; Horstmann et al., 2010; Guye, Bettus, Bartolomei, & Cozzone, 2010). In particular, graph analysis has been proposed to be promising in analyzing brain complex network in epilepsy (Onias et al., 2014). The brain’s functional network architectural features have been found associated with epileptic seizures (Reijneveld, Ponten, Berendse, & Stam, 2007), and previous research using graph theory analysis found abnormal functional network during absence seizures (Ponten, Douw, Bartolomei, Reijneveld, & Stam, 2009). Moreover, graph theory analysis was found effective to analyze the complexity of antiepileptic drugs (AED) administration patterns in children with epilepsy (Ibrahim, Rutka, & Snead, 2013).

Graph properties measure the topological features of a node in the complex network, which were frequently used in graph theory analysis. Some typically used graph properties include strength, clustering and centrality, respectively indicating the overall connectivity, embeddedness, and ‘hub-ness’ of a node. Some previous studies involved graph properties in their analysis of epilepsy: Higher clustering coefficient was found during mesial temporal lobe seizures, indicating neural network with more ordered configuration during seizures (Ponten, Bartolomei, & Stam, 2007). Increased clustering coefficient and altered distribution of hubs were found in patients with temporal lobe epilepsy (Bernhardt, Chen, He, Evans, & Bernasconi, 2011). Clustering coefficient and functional connectivity (average phase lag index, PLI) are negatively associated with the duration of pharmaco-resistant temporal lobe epilepsy (Van Dellen et al., 2009). ‘Betweenness centrality’ was found associated with the location of the resected cortical regions in patients with epilepsy who were seizure-free following surgical intervention (Wilke, Worrell, & He, 2011, p. 84).

In the present study, the graph property of strength, clustering and centrality were used to in the analysis of brain network features within the sensorimotor cortex. The graph property of strength represents the sum of all neighboring link weights of one particular node (or region) in
the network, indicating the overall connectivity of a node (Rubinov & Sporns, 2010). Clustering represents the fraction of a node’s neighbors that are also neighbors of each other, indicating embeddedness of a node (Rubinov & Sporns, 2010). Centrality represents the number of the shortest paths all other nodes in the network passing through a particular node, indicating hubness of a node (Bullmore & Sporns, 2010).

The Network-based Statistic (NBS) is an approach based on graph theory analysis to identify synchronization network in a graph in case-control and task dependent studies, or in calculating correlations with other neuropsychological measures (Zalesky, Fornito, & Bullmore, 2010). It has been proven its utility in identifying connectivity network in case-control studies involving various disorders such as schizophrenia, major depressive disorder, Alzheimer's disease, ASD, and ADHD (Zalesky, Fornito, & Bullmore, 2010; Zalesky et al., 2011; Zhang et al., 2011; Wang et al., 2013; Li et al., 2014; Cocchi et al., 2012). The present study aims to use NBS to identify neural synchronization network following median nerve stimulation to children with epilepsy.

7 Research Questions of the Present Study

Neural synchronization, especially in gamma band, plays an important role in a variety of human brain cognitive and motor functions. In particular, in childhood epilepsy, alteration of gamma activity and synchrony within the sensorimotor cortex has been found to be related to motor difficulties. Based on these findings, the present study aims to further investigate gamma-band neural synchronization, especially within sensorimotor system, in childhood epilepsy and its associations with motor impairments in the patients.

Previous studies related to neural synchronization within sensorimotor cortex in childhood epilepsy and its association with motor functions have either investigated gamma-band intracranial EEG synchronization during ictal periods in childhood epilepsy and its association with motor impairments (Ibrahim et al., 2012), or examined gamma-band activity MEG amplitude within primary motor cortex following median nerve stimulation in children with
epilepsy (Doesburg et al., 2013). No previous research, however, investigated gamma-band neural synchronization following median nerve stimulation in children with epilepsy and its association with motor impairments. The present study, thus, used MEG recordings during median nerve stimulation in children with epilepsy to investigate the hypothesis that altered inter-regional gamma band synchronization within the sensorimotor network are related to motor performance difficulties.

8 Research Hypotheses of the Present Study

The hypotheses of the present study are (1) stimulation of the median nerve increases gamma-band synchronization within the sensorimotor network. (2) The neural synchronization network following median nerve stimulation will primarily involve synchronization of primary motor cortex and primary somatosensory cortex contralateral to the stimulated arm. (3) The involvement of primary motor cortex and primary somatosensory cortex in the stimulation-dependent synchronization network is associated with the motor difficulties of the children with epilepsy.
1 Participants

The study involved 99 children and adolescents with epilepsy, including 42 females and 57 males. The age range was 8 – 19 years old with mean age 13.87 (± 2.64) years old. These data were collected from patients undergoing evaluation for possible resective surgery for drug-resistant epilepsy at the Hospital for Sick Children. The participants’ ages of seizure onset ranged from 0 to 16 years old with mean age of onset 6.95 (± 4.43) years old. The duration of epilepsy ranged from 0.42 to 15.86 years with mean duration 7.17 (± 4.37) years. The participants included 45 with seizure focuses in left hemisphere, 37 in right hemisphere, 2 in two hemispheres and 15 with unknown records. The seizure focuses of the participants included temporal (in 33 participants), frontal (in 14 participants), central (in 5 participants) and other combined focuses like frontal-temporal-parietal, temporal-parietal and so on. The participants included 81 right-handed people, 16 left-handed people and 2 with unknown records of handedness. Their median nerve stimulation and MEG scanning dates ranged from January 28th, 2004 to October 15th, 2014. The neuropsychological tests dates ranged from December 22nd, 2004 to October 27th, 2014. For participants undergoing multiple MEG scans on multiple dates, data from the scans closest in time to neuropsychological testing was chosen for the analysis. All the participants did not have major neurological abnormalities that would prevent adequate coverage of brain-wide networks (due to prior resection or other reasons) observed from their magnetic resonance imaging (MRI) images. All participants were scanned at the Hospital for Sick Children. The study was reviewed and approved by the Hospital for Sick Children Research Ethics Board.
2 Median Nerve Stimulation and MEG Data Acquisition

Median nerve somatosensory evoked fields (SEF) were obtained from electrical stimulation (4Hz supra-motor threshold) of both left and right arms in the participants while the MEG data were recorded (Figure 1). Each participant may have undergone multiple stimulation runs in a scan but due to the clinical standards some runs were excluded (motor threshold not attained, child moved, unusual artifact, etc). Only one run for each arm for each subject was selected in a scan. Each run included 400 trials. A trial length of 200ms with a 50ms pre-stimulation baseline was used for analysis. To facilitate accurate co-registration of MEG activity to brain anatomy, a T1 weighted anatomical volumetric MRI was collected for each participant following MEG recording.

![Figure 1: Median Nerve Stimulation](image)

3 Neuropsychological Data Acquisition

The participants underwent three neuropsychological tests to examine motor abilities: the grooved pegboard test, finger tapping test and grip strength test. In the grooved pegboard test, the participants were asked to put pins into the holes on the pegboard quickly following some particular guidance (Espe-Pfeifer & Wachsler-Felder, 2000). In the finger tapping test, the participants were asked to keep their palms immobile on aboard with a key connected to a
counter and to tap their index fingers on the key as fast as possible (Schatz, 2011). In the grip strength test, the participants were required to hold the dynamometer in the hand with the arm straight by the side of the body.

Raw scores of the tests were transformed to z-scores based on age norms for the analyses. The extreme scores (in z-scores) in the tests were excluded from the analysis tests (beyond three standard deviations plus and minus the mean scores). Not every participant did all three tests as these were selected according to the clinical management needs of each patient. Accordingly, the final numbers of participants used in the correlation tests were 92 for the grooved pegboard test, 78 for the finger tapping test, 81 for the grip strength test in left hand and 86 for the grip strength test in right hand.

4 Data Analysis

116 virtual sensors representing all cortical, subcortical and cerebellar sources in the Automated Anatomical Labeling (AAL) atlas were reconstructed using beamformer analysis: Firstly, MEG data were co-registered with MRI data by aligning the fiducial markers, and a multisphere head model was constructed for each subject using the individual MRIs (Lalancette, Quraan, & Cheyne, 2011). MRIs were then normalized into standard MRI space using Statistical Parametric Mapping 2 (SPM2) (Ashburner & Friston, 1999). Seed locations, which were 116 cortical and sub-cortical locations for source-space MEG analysis were unwarped from standard MRI space into the corresponding location in head space for each individual (Tzourio-Mazoyer et al., 2002). Broadband time-series representing the activity of each of the 116 sources were then reconstructed for each trial using scalar beamformer analysis. Scalar beamformer analysis was used to estimate the activity at each source while maximally suppressing signals from other sources, including ocular and muscle artifacts (as a spatial filter) (Cheyne, Bakhtazad, & Gaetz, 2006; Cheyne, Bostan, Gaetz, & Pang, 2007).

Data were filtered from 30 to 80 Hz (gamma band) and the Hilbert transform was used to obtain time series of instantaneous phase values for each trial and reconstructed brain region.
The phase lag index (PLI) in 30 – 80 Hz was calculated to index phase synchronization between each pair of sources at each time point, producing a connectivity matrix for each time point (averaged among all the participants). The connectivity matrix corresponding to each time point within a whole trial constituted a ‘connectivity movie’ showing connectivity dynamics during a trial.

A trial length was divided into 500 time points in the analysis, and pre-stimulation baseline was defined as 0 – 50 ms (0 – 125 in time points) in a trial starting from the stimulation onset. Stimulation active window was defined as a time period with the same length as pre-stimulation baseline but with highest average connectivity observed from connectivity matrix and connective movie. In the present analysis, it was defined as 60 -110 ms (150 – 275 in time points) in a trial starting from trial onset.

Differences in inter-regional gamma synchrony during stimulation active window, relative to a pre-stimulation baseline, were assessed using the network based statistic (NBS) (Zalesky, Fornito, & Bullmore, 2010). Synchronization networks corresponding to stimulation to both arms and stimulation to either left or right arm were both analyzed.

The graph properties of strength, clustering and centrality were analyzed to indicate the overall connectivity, embeddedness, and ‘hub-ness’ respectively of the primary motor and somatosensory cortex in the stimulation-dependent network using the Brain Connectivity Toolbox (Rubinove & Sporns, 2010).

Correlations between scores of the three neuropsychological measures and graph properties from the primary motor and somatosensory cortex in the contralateral hemisphere were investigated using Matlab.
Chapter 3
Results

1 Primary Motor and Somatosensory Cortex Had Strong Connectivity with Other Regions Following Median Nerve Stimulation

The connectivity movie consisting of connectivity matrix for each time point in a trial showed that the primary motor and somatosensory cortex had relatively stronger 30-80 Hz inter-regional phase synchronization with other sources during the stimulation active window. Overall, the mean connectivity of all sources kept stable during pre-stimulation baseline window and increased steeply after 60 ms, reaching a peak at around 70 ms and then gradually decreased to a baseline level (Figure 2).
In the connectivity matrix, each cell represented the phase synchronization index between a pair of sources at a time point. The above figure shows the time point corresponding to the red line in the right panel;

(2) Warmer colors of a cell represented stronger connectivity of pairs of sources had. Source number 1 and 2 in the matrix represented left and right primary motor cortex (precentral gyrus). Source number 57 and 58 represented left and right primary somatosensory cortex (postcentral gyrus);

(3) Besides of the primary motor and somatosensory cortex, source number 19, 20 and 33, 34 also had relatively strong connectivity with other sources. Source number 33 and 34 represented left and right middle cingulum. Source number 19 and 20 represented left and right supplementary motor areas.
2 Stimulation Dependent Gamma-band Network Synchronization Involved Primary Motor and Somatosensory Cortex and the Network was Lateralized

Stimulation dependent gamma-band network synchronization following median nerve stimulation to both arms involved the primary motor and somatosensory cortex (Figure 3).

Figure 3: Stimulation Dependent Gamma-band Network Synchronization Following Median Nerve Stimulation

(1) Threshold in NBS: 15.0;

(2) Other nodes in the network (other than primary motor and somatosensory cortex): left inferior parietal lobe, left and right supra marginal gyrus.

The synchronization network analysis involving stimulation from only one arm found lateralization of the synchronization network contralateral to the arm of stimulation. The contralateral primary somatosensory cortex was found in synchronization network following
stimulation from only one arm (either left or right) and serves as a ‘hub’ node connecting to all the other nodes in the network\textsuperscript{4, 5}.

3 Lateralization of Graph Properties of Primary Motor and Somatosensory Cortex

The lateralization of network connectivity depending on the arm of stimulation was found in the strength, clustering and centrality of the primary motor and somatosensory cortex (Figure 4 and Figure 5).

\textsuperscript{4} Threshold in NBS used in the analysis involving stimulation from left arm: 13.8;

Nodes involved in the synchronization network other than the right somatosensory cortex: right superior temporal pole, right middle temporal pole, right parahippocampal gyrus, right hippocampus, right amygdala, left supramarginal gyrus, left inferior parietal lobe.

\textsuperscript{5} Threshold in NBS used in the analysis involving stimulation from right arm: 13.8;

Nodes involved in the synchronization network other than the left somatosensory cortex: left superior parietal lobe, left inferior temporal lobe, left thalamus, left parahippocampal gyrus, right inferior parietal lobe, right middle occipital lobe, right inferior frontal opercular area, right angular gyrus
Figure 4: Time Course of Lateralization of Graph Properties of the Primary Motor and Somatosensory Cortex (Baseline-Corrected)
To examine whether the handedness of the participants had impact on the lateralization of graph properties, t-tests were done. No significant differences were found between left-handed and right-handed participants on the graph properties of primary motor and somatosensory cortex in either hemisphere following stimulation from either arm.

Besides, to examine whether the epileptic hemispheres of the participants had impact on the lateralization of graph properties, t-tests were done. Participants with left hemispheric seizures were found to have significant stronger strength ($t(80) = 2.083, p = 0.040$), centrality ($t(80) = 1.995, p = 0.049$) and marginally significant clustering ($t(80) = 1.893, p = 0.062$) in right primary motor cortex following left-arm stimulation than the participants with right
hemispheric seizures. No significant differences were found between participants with left and right hemispheric seizures on the other graph properties of primary motor and somatosensory cortex in either hemisphere following stimulation from either arm.

4  **Graph Properties of Primary Motor and Somatosensory Cortex were Associated with the Grooved Pegboard and Finger Tapping Performance**

Table 1 below shows the results of the correlation tests between graph properties of primary motor and somatosensory cortex and motor performance. Significant associations between graph properties of primary motor and somatosensory cortex and motor performance on the grooved pegboard and finger tapping tests for the contralateral hand were observed (Figure 6: associations with pegboard test performance. Only centrality in left primary motor cortex was significantly associated with finger tapping test performance in right hand $r = 0.2578 \ p = 0.0222$ so it was not shown in figures).

<table>
<thead>
<tr>
<th>Test Type (Hand of the test)</th>
<th>Node (which Stimulation Arm)</th>
<th>Graph Property Type</th>
<th>$r$</th>
<th>$p$</th>
</tr>
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<tbody>
<tr>
<td>Grooved Pegboard (left hand)</td>
<td>Right Primary Motor Cortex</td>
<td>Strength</td>
<td>0.286</td>
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<td>(left arm stimulation)</td>
<td>Clustering</td>
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<tr>
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<td>Right Primary Somatosensory Cortex</td>
<td>Centrality</td>
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<td>0.0389*</td>
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<tr>
<td></td>
<td>(left arm stimulation)</td>
<td>Strength</td>
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<td>0.0135*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clustering</td>
<td>0.2793</td>
<td>0.007**</td>
</tr>
</tbody>
</table>

Table 1: Correlations between Graph Properties of the Primary Motor and Somatosensory Cortex and Motor Performance for the Contralateral Hand
<table>
<thead>
<tr>
<th>Task</th>
<th>Region</th>
<th>Centrality</th>
<th>Strength</th>
<th>Clustering</th>
</tr>
</thead>
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<tr>
<td>Grooved Pegboard</td>
<td>Left Primary Motor Cortex (right hand)</td>
<td>0.1812</td>
<td>0.1866</td>
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<td></td>
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<td>Finger Tapping</td>
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<td></td>
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<td>0.5928</td>
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<table>
<thead>
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<th>(right arm stimulation)</th>
<th>Clustering</th>
<th>Centrality</th>
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<td>0.4553</td>
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<tr>
<td>Centrality</td>
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<td>0.2781</td>
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</table>

*: p < 0.05 **: p < 0.01 ***: p < 0.001

Figure 6: Correlations between Graph Properties of the Primary Motor and Somatosensory Cortex and Pegboard Results for the Contralateral Hand
To examine whether handedness of the participants had impact on their motor performance of different hands, t-tests were performed and no significant differences between left-handed and right-handed participants on all three types of motor tests performance in either hand were observed.

Besides, to examine whether hemispheres of seizures of the participants had impact on their motor performance of different hands, t-tests were performed and no significant differences between participants with left and right hemispheric seizures on all three types of motor tests performance in either hand were observed.
Chapter 4
Discussion

As hypothesized, it was found that the primary motor and somatosensory cortex were involved in the gamma-band neural network synchronization network following median nerve stimulation in children with epilepsy. Furthermore, lateralization of the gamma-band synchronization network was found depending on the arm of stimulation in this study and lateralization was also found in the graph properties (strength, clustering and centrality) of the primary motor and somatosensory cortex. Finally, the significant correlations between graph properties of primary motor and somatosensory cortex and motor performance in pegboard and finger tapping tests for the contralateral hand were found. The findings primarily answered the research questions the present study raised and confirmed our research hypotheses.

The present study uniquely used median nerve stimulation paradigm in children with epilepsy and found some effects congruent with previous literatures: the present stimulation dependent synchronization network involving primary motor and somatosensory cortex are congruent with the previous findings that median nerve stimulation could induce neural synchronization within sensorimotor cortex (Della Penna et al., 2004). The present finding of lateralization of the simulation dependent synchronization network is congruent with the previous finding of the dominant role of the contralateral hemisphere in somatosensory information processing from median nerve stimulation (Nikouline et al., 2000).

The present study uniquely found significant associations between network synchronization within sensorimotor cortex induced by median nerve stimulation and motor impairments in children with epilepsy. Previous research relating to neural synchronization in epilepsy primarily investigated the association between neural synchronization and seizures (Bartolomei et al., 2005; Schindler, Leung, Elger, &Lehnertz, 2007; Arthuis et al., 2009; Lemieux, Daunizeau, & Walker, 2011) or between neural synchronization and epileptogenic brain areas (Ochi et al, 2007; Jacobs et al., 2008; Ortega, Menendez, Sola, & Pastor, 2008; Warren et al., 2010; Akiyama et al., 2011). Few studies investigated the relationship between neural synchronization in patients with epilepsy and their motor abilities (Zhang et al., 2009b; Ibrahim...
et al., 2012). In previous research, significant associations between neural synchronization and motor impairments in children were found during ictal periods using intracranial electroencephalographic (iEEG) recordings (Ibrahim et al., 2014). The present study, however, was the first to use median nerve stimulation paradigm and MEG recording to investigate this association.

Some limitations, however, exist in the present study. One was the lack of control group, which limited our explanation of the degree of alteration of neural synchronization within sensorimotor cortex and whether the association between neural synchronization and motor abilities was unique to children with epilepsy.

One unanswered question raised by the results of the present study was that the significant correlations between graph properties of primary motor and somatosensory cortex and motor performance were only found with the motor tasks of grooved pegboard and finger tapping, but not grip strength test. Moreover, in the finger tapping test, only performance in one hand (right hand) was significantly associated with one graph property (centrality) in left primary motor cortex. And in the grooved pegboard test, performance in left hand had more significant correlations with graph properties than right hand.

One explanation for why more significant associations between graph properties and the grooved pegboard test performance than for finger tapping and grip strength tests was that the grooved pegboard test is a more complicated form of motor task than other motor tests including finger tapping and grip strength tasks (Merker & Podell, 2011). The grooved pegboard test requires sensory motor integration and high-level motor processing (Roy & Square-Storer, 1994). Thus, the alterations of functional connectivity brain network in childhood epilepsy might be more sensitive to high-level motor processing abilities.

One explanation for why the grooved pegboard test performance in left hand had more significant correlations than right hand was that difference of performance between left and right hand were observed in the grooved pegboard test (Bryden, Roy, Rohr, & Egilo, 2007). Besides, asymmetries between the sources activated in the left and right hemispheres following
median nerve stimulation, as well as asymmetric response amplitudes within somatosensory cortex between two hemispheres following median nerve stimulation were found (Rossini et al., 1994; Forss et al., 1994), which may also contribute to the different correlations between the left-hand and right-hand grooved pegboard performance with the graph properties in the contralateral hemisphere following median nerve stimulation.

Another question found in the present findings was that the participants with left hemispheric seizures were found to have significant or marginally significant stronger graph properties in right primary motor cortex following left-arm median nerve stimulation than the ones with right hemispheric seizures. No significant differences, however, were found in graph properties in other regions between participants with left and right hemispheric seizures. The finding may indicate the unique influence of epileptic seizures on the response patterns in right primary motor cortex following median nerve stimulation from contralateral arm. Since the significant results were only found in the left primary motor cortex but not the right one, it may be also influenced by the asymmetric interhemispheric responses following median nerve stimulation (Rossini et al., 1994; Wikström et al., 1997). This finding was also partly congruent with the previous research indicating localized hemispheric lesions may further influence asymmetric responses following median nerve stimulation (Yamada, Kimura, Young, & Powers, 1978; Yamada, Kayamori, Kimura, & Beck, 1984). However, since the present study involved the similar number of participants with left and right hemispheric seizures, it may partly diminish the influence of lesions in different hemispheres on the graph properties.

Another remaining question resulting from the present findings was the stimulation dependent gamma-band network synchronization following median stimulation from either left or right arm involved nodes located in temporal and inferior parietal regions. This result seems to be contradictory to the previous findings that SEF sources activated from median nerve stimulation mainly involve the outer aspect of the hemispheres (primary and secondary somatosensory cortex) (Mauguiere et al., 1997). It was found in previous research, though, that posterior parietal cortex could be possibly activated from median nerve stimulation (Fross et. al., 1994), which may be corresponding to what we found in the present study that the inferior parietal regions were involved in the network synchronization.
One explanation of why the temporal and inferior parietal regions were found in stimulation dependent network for one arm is that the present study aimed to find synchronization networks, and furthermore NBS was an approach to find connections in large-scale brain networks based on “traditional cluster-based thresholding of statistical parametric maps” (Zalesky, Fornito, & Bullomore, 2010, p. 1197). Accordingly, the mechanism of identifying sources in the network may differ from identifying the sources of activation and thus it led to findings seeming to be incongruent of the previous research.

In conclusion, the present study found involvement of the primary motor and somatosensory cortex was in the network synchronization following median nerve stimulation in children with epilepsy. Involvement of primary motor and somatosensory cortex in distributed network synchronization was associated with motor difficulties in this group. These findings are congruent with the view that epilepsy may lead to performance deficits through the disruption of connectivity in functional brain networks.


