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Disrupted small-world brain network in children with Down Syndrome

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HIGHLIGHTS

- The first study on global organization of the functional brain connectivity (FBC) in DS.
- FBC of the DS and normal children are topologically different in theta and alpha bands.
- The topological abnormalities are primarily in upper alpha within left hemisphere.

ABSTRACT

Objective: To explore how the global organization or topology of the functional brain connectivity (FBC) is affected in Down Syndrome (DS).
Methods: As the brain is a highly complex network including numerous nonlinearly interacted neuronal areas, the FBCs of typically developing (TD) children and DS patients were computed using a nonlinear synchronization method. Then the differences in global organization of the obtained FBCs of the two groups were analyzed, in all electroencephalogram (EEG) frequency bands, in the framework of Small-Worldness Network (a network with optimum balance between segregation and integration of information).
Results: The topology of the functional connectivity of DS patients is disrupted in the whole brain in alpha and theta bands, and especially in the left intra-hemispheric brain networks in upper alpha band.
Conclusions: The global organization of the DS brain does not resemble a Small-World network, but it works as a random network.
Significance: It is the first study on global organization of the FBC in DS.

1. Introduction

Down Syndrome (DS) is caused by triplication of the human chromosome 21. It is a relatively common genetic disorder with an approximate prevalence of 1 in 800 babies born alive in the world (Nadel, 2003). DS causes lifelong mental retardation and developmental delays especially in language as well as learning deficits (Carlesimo et al., 1997; Gardiner et al., 2010; Næss et al., 2011; Silverman, 2007; Vicari et al., 2000, 2002). Many neuroimaging studies have reported global deficits of the DS brain, both structurally and functionally. The number of dendritic spines, latency afferent inhibition in motor cortex, total brain volume, total gray matter, and total white matter volumes of DS patients are smaller than typically developing (TD) age-matched subjects (Kojima and Shirao, 2007; Marin-Padilla, 1976; Martin et al., 2012; Menghini et al., 2011; Nardone et al., 2006; Pinter et al., 2001). Also, slow-wave brain (higher activity in lower frequencies and lower activity in higher frequencies) (Babiloni et al., 2009, 2010), low frequency of individual alpha peaks (Velikova et al., 2011), and low mean power of alpha frequencies (Kaneko et al., 1996) are the major characteristics of the DS brain's electrical activity, detected by electroencephalogram (EEG).

Functional connectivity plays an essential role in the flowing of information among brain networks, accomplishing cognitive tasks. Deficient functional brain connectivity (FBC) has been reported in many different neuropsychiatric and neurologic disorders, such as autism (Ahmadlou et al., 2012e) and Alzheimer's disease (Jeong, 2004; Greicius, 2008; Dauwels et al., 2010a,b). However, there are few studies focusing on analysis of FBC in the DS brain. Schmid et al. (1992) using coherence analysis in the resting eyes-open state, found higher and lower intra-hemispheric synchronization of DS brain delta and alpha EEG bands, respectively. They also found significant differences between inter-hemispheric fronto-central synchronization of DS and TD subjects in particular age ranges in both eye-closed and eyes-open conditions. McAlaster

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(1992) found significant differences of coherence between the two groups based on their EEGs in eyes-closed resting state. The greatest between-group differences they reported were in the left hemisphere and in the posterior cortical regions. Babiloni et al. (2009) using a method, called direction transfer function (DTF), showed an abnormally opposite direction (left to right) of inter-hemispheric functional connectivity (in occipital lobe) in young DS in eyes-closed resting state.

However, all of the aforementioned studies have analyzed FBC of the DS brain locally (analyzing the connectivity only within and between brain regions), and not globally; whereas global properties of the FBC are also of importance for efficient information flow and may be affected in DS as well. Also, to the best knowledge of the authors, all of the aforementioned results of the FBC analyses (i.e. coherence and DTF) come from regarding the brain as a simple linear system, whereas the brain is a highly complex and nonlinear network of large numbers of interacted neurons (Ahmadi et al., 2013; Ahmadlou et al., 2012c,d; Mamashli et al., 2010). Therefore analysis of FBC using nonlinear measurements may be closer to the nature of the brain, conceptually, and may thus reveal other aspects of the FBC (Ahmadlou and Adeli, 2011b). In the present study, using a nonlinear synchronization measurement, called Visibility Graph Similarity (VGS) (Ahmadlou and Adeli, 2012), the DS's FBC was determined and its global structure analyzed in the light of the "Small-Worldness" concept. A Small-World (SW) network has a nearly, if not completely, optimum structure which is defined as a balance between local and global structural characteristics (Watts and Strogatz, 1998). Such structural balance leads to an optimal balance between segregation and integration of information in the network. SW network is characterized by coexistence of dense clustering of connections and short path lengths among the network units (Bassett, 2006; Liu et al., 2008; Sporns and Zwi, 2004; Watts and Strogatz, 1998). The SW network has the highest synchronizability and the highest speed of information transmission among the network functional units, compared with other types of network structures such as random, lattice, and ordered networks. Recent research indicates that normal neocortex and different areas in the brain have SW structures (Bassett, 2006; Park et al., 2008; Sporns and Zwi, 2004; Stam and van Straaten, 2012). The deficient SW brain network has been reported in many neuropsychiatric and neurologic disorders, such as attention deficit/hyperactivity disorder (Ahmadlou et al., 2012a,b), Alzheimer's disease (Liu et al., 2012; Stam et al., 2007), schizophrenia (Liu et al., 2008; Ma et al., 2012), major depressive disorder (Zhang et al., 2011), substance abuse disorder (Yuan et al., 2010) and mild cognitive impairment (Liu et al., 2012; Wang et al., in press).

This paper investigates the organization of the overall and hemispheric FBCs of children with DS, at different EEG sub-bands, in the framework of Small-Worldness with the purpose of discovering how the topology of the FBC is affected in DS.

2. Background: Graph Theory and Small-World network

The SW characteristics are usually computed using Graph Theory (GT), in which the network units and the connections between the pair-units are modeled as vertices and edges, respectively. Fig. 1 illustrates the procedure of transformation of an example 19-channel digital EEG set (Fig. 1a) into its connectivity graph (Fig. 1c). Connectivity coefficients between channel pairs are measured and placed in the arrays (squares) of a 19 × 19 FBC matrix (Fig. 1b). The light intensity of each array represents the strength of the connectivity. In Fig. 1c the darker intensity indicates a greater value in the connectivity matrix of the FBC graph (Ahmadlou and Adeli, 2011a).

The key topological characteristics of a weighted complex graph are the clustering coefficient (C) as an indicator of the local structure (C varies from 0 to 1), and the mean path length (L) as an indicator of the global structure of the network (L varies from 1 to the number of nodes in the graph). A SW network is characterized by coexistence of a high C and a low L. In contrast, a random network has a low C and a low *L* simultaneously, and regular networks have a large C and a large *L* simultaneously (Bullmore and Sporns, 2009; Smit et al., 2008; Watts and Strogatz, 1998). It means in the

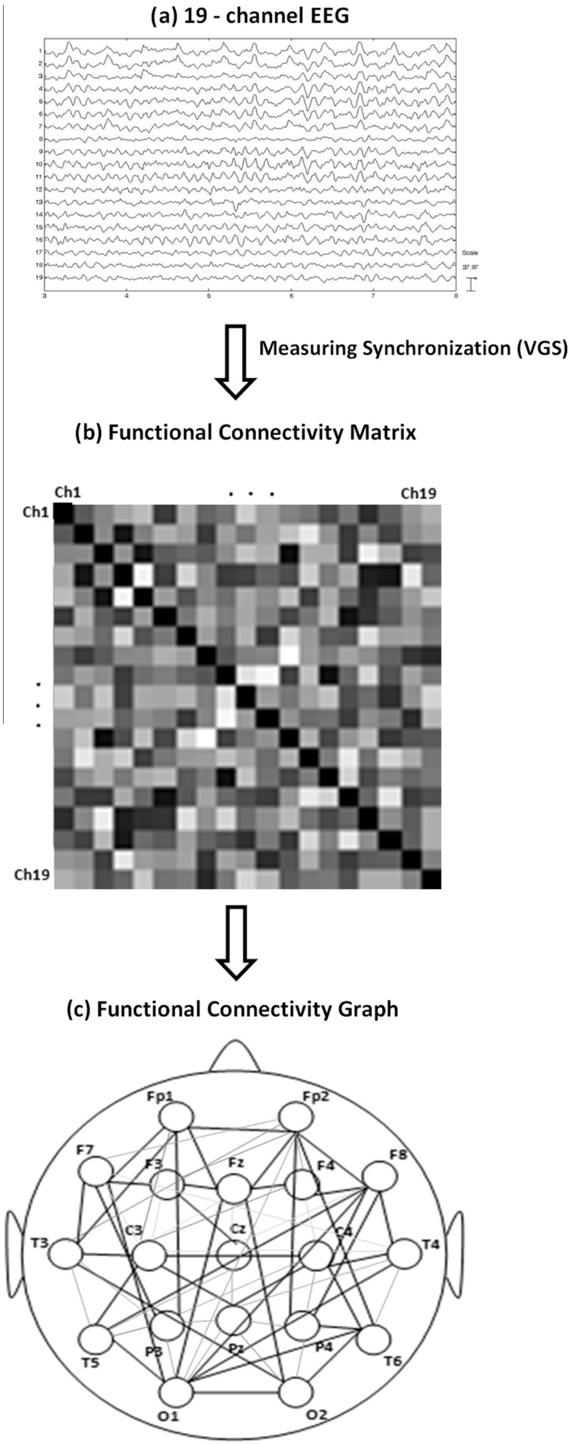

Fig. 1. Illustration of the conversion procedure of a 19-channel EEG to its functional connectivity graph (adapted from Fig. 1 of Ahmadlou et al. (2013), with permission).