# 論 文 の 内 容 の 要 旨

論文題目　　MEG Study on Abnormal Development of Brain Network in Autism Children
（自閉症児における脳ネットワークの発達異常に関するMEG研究）

氏　　名　　段　放

This thesis studies the brain network of children with autism spectrum disorder (ASD). Magnetoencephalography (MEG) data were recorded to analyze the brain function due to its characteristics friendly with children. MEG is a kind of non-invasive and real-time functional neuroimaging technique. MEG possesses good temporal resolution in the millisecond and appropriate quantity of channels. ASD is a range of neurodevelopmental disorders. Except a few of individuals with autistic savantism can show extraordinary skills in music, photographic memory etc., most of ASD individuals are suffering communication disorder, logopathy and learning disorder. Recently, the changing in the diagnosis criterion of ASD encourages the early diagnosis. The study of ASD children in pre-school age becomes more meaningful. Popular research technique in brain network analysis, namely graph theory, is introduced to study the network development of ASD children. The MEG sensors are considered as the nodes and the correlation, coherence, and synchronization between sensors are taken into account to decide the edges. Our focus is to find insight by the graph indices of brain graphs to understand the development tendency of functional network ASD children.

The artifacts removal method for obtaining high quality MEG data is shown in Chapter 2. I present the classification method for automatic removing artifacts from MEG data. I propose a method that is weighted support vector machine (WSVM) with reweighting procedure to handle the imbalance independent components (ICs) dataset and boost specificity of classifier by re-weighting the sample's weight of the negative class. The advantage of the proposed method is shown by experiments on a manually marked MEG ICs dataset. SVM with Gaussian kernel is applied to classify features. The weight of each sample is updated based on the specificity of classifier. Experimental results on manually marked MEG dataset showed that the method can correctly distinguish the artifacts from the MEG ICs. Nearly all the MEG ICs are preserved. The classification accuracy is 97.91%. I find that the method is not sensitive to individual difference. The classifier which is well trained by sufficient dataset can be applied on the MEG data of other individuals.

After the preparation of high quality MEG data, the brain graphs of broadband MEG of ASD and typically developing (TD) children are analyzed in Chapter 3-5. Both direct comparison between ASD and TD children and the network developments of two groups are studied. To study the network development, raw scores of the Kaufman Assessment Battery for Children (K-ABC) are employed as cognitive performance indices.

In Chapter 3, network level analysis is performed on TD children and finds a baseline of network development in free video watching task. As a compromise, the MEG data of children were recorded during free video watching by a custom-made, child-sized MEG. New baseline of which is the relevance between network structure and cognitive performance need to be found. The networks of TD children are analyzed by indices in small-world model. Extensive researches on the resting state, including health and clinical studies, have shown that brain network of human is organized as a small-world network. Studies on resting and working state networks of health adults suggested that intelligence and cognitive performance may be predictors of various parameters of the small-worldness. Previous research of children showed that brain network possesses small-world organization similar to that of young adults. The small-worldness of children's brain graphs in a working state has not yet been well characterized. Therefore, I intent to employ the small-world model to analyze the MEG data of TD children during free viewing of video and draw a new baseline for further clinical study on ASD children. I find that the small-worldness of network was negative correlated with the simultaneous processing raw score, a measure of visual processing (Gv) ability. The free viewing of video is proved to be a task mainly involved visual processing. The networks which are possessed by the children with high simultaneous processing raw scores can be more efficient on the information processing in local area than the low score children. The baseline is that, under free viewing of videos, brain network adjust its structure from its strongest small-world state to a state that the connections become clustered in local areas such as the frontal and occipital lobes. It might be a more useful state for handling visual processing task.

In Chapter 4, I analyze the network of ASD and TD children by network, nodal, and edge level indices. The network level analysis is done by indices of small-world model. Specific regions of network are learned by nodal level indices, nodal degree and nodal efficiency. The directly comparison between ASD and TD on network and nodal levels do not show significant difference. I study the network development of ASD and TD children by using K-ABC scales as reference. The network level results show that ASD children hold atypical network development and lost the ability of rebalance of local and global connections during the task. Specific development regions are found by nodal and edge level studies. Group-specific development related edge is defined to study the edge level information. ASD children show negative development in their left frontal area. This may cause the rightward phenomenon of very young ASD children. Comparing with ASD children, TD children can balance their network between hub area, parietal area, and their sensory lobes, left temporal-occipital area and right parietal-temporal area well. Positively developing edges in frontal area also indicate the well information integration ability of TD children. The similar developing pattern between ASD and TD show by simultaneous processing scale imply that good capabilities associated with the right developing direction.

In Chapter 5, I analyze network of ASD and TD children on area level. I introduce three indices to study ASD and TD children under the framework of graph theory. First index, namely cross area index, is inspired by modularity in complex network study. Other two indices, average path length and sub-graph clustering coefficient, are derived from small-world model. The cross area index and average path length can study the interaction between regions without cutting out the target regions from the rest of network and considering the interaction of target regions as a part of brain. Previous studies of interaction between regions shared a common trick, i.e., only consider the data of two regions those are chosen. The indices I introduce in this chapter do not separate the target regions from the whole network but consider the interaction between regions in the network. By combining the area level indices, I interpret the data from aspects of whole network. First, I find that the decrease of nodal efficiency of temporal-parietal-occipital (TPO) area in TD group also could decrease the information interference of TPO area by rest of the brain. Second, the network of posterior part of ASD children may easily develop a rigid grid with more nearby connections. Third, the frontal and parietal of TD children develop a network with better information transmission path and information exchange with rest of brain. Meanwhile, posterior area and anterior area interaction develop to a structure with long path length and stronger independence of information processing.

In Chapter 6, I filter the MEG data into eight wave bands, 0.7–3.9 Hz (delta), 4–8 Hz (theta), 8–9.9 Hz (alpha1), 9.9–12.1 Hz (alpha2), 12.1–19.9 Hz (beta1), 19.9–29.9 Hz (beta2), 29.9 – 60 Hz (gamma1), and 61.0–80 Hz (gamma2), and study the brain network of each band. I apply the network, area, nodal and edge level indices on the band-passed MEG data. In the direct comparison between ASD and TD group, ASD children show strong local clustering in gamma1 and gamma2 bands. Then, network development study finds atypical network development rhythms based on the reference of simultaneous processing scale. The network development in delta, alpha2, beta1, beta2, and gamma2 band network shows abnormal patterns in ASD children. In delta band, I cannot find the positively developing of nodal efficiency and degree of node in forehead of ASD, which can be observed in TD children. I assume that the deficit of attention may relate to the atypical development of delta band forehead network. Alpha2, beta1, and beta2 bands show similar network developing patterns in ASD group. The positive development is found in central-parietal area where the motor cortex is. I suggest that the positive development in central-parietal area of ASD children in beta-nearby bands is caused by gradually dysfunction of mirror neurons. To more forward, the positive development in central-parietal area of ASD children may cause the impairment of understanding the actions of other people. The gamma band results suggest that the network of ASD children in gamma band possess more local cluster than TD children. It is compatible with several studies those showed abnormal gamma oscillations. ASD children do not have strong negatively developing on nodal efficiency and degree of node which is found in TD group. I suggest that the ASD children lose the rebalance process of excitatory and inhibitory neurons, and result the atypical gamma band network development. It is surprise that the significant different edges between ASD and TD children are found in right frontal area and the connecting strengths of ASD children are stronger than TD children. This phenomenon can be found in several bands. Strong connecting strength may not mean efficient information processing. It may relate to information block, because other study suggested that ASD participants process more information than TD.

In Chapter 7, I employ the characteristics of brain graph of ASD which are found in previous chapters as neuromarkers to classify ASD and TD children. Both raw network features and the development related network features are used to classify ASD and TD children. The SVM with linear kernel is used as the classifier. I select the features by r-square index. The biggest challenge of this part of study is that I merely find significant differences between groups on their network indices. The reason may associate with the task of experiment and the stage of ASD of pre-school children. To overcome this difficulty, the network development features play a key role in the classification. The features with high r-square are all features of network development. By using the development indices, e.g. the age and raw scores of K-ABC scales, the classification accuracy is improved. The selected features with high r-square are compatible with the atypical network developing rhythms. The accuracies of nodal-network level indices and area-network level indices proof that the method is work. When the number of feature is 22, the classification accuracy of area-network level age-related development features is 86.83％. The results of area and network level features indicate that the classification accuracy deteriorate if the development index, age, is not involved. The classification accuracy of using raw area-network level features only is 76.33％. Compared with raw network features, the diagnostic yield of ASD by network development features is increased more than 10%.

In Chapter 8, I summarize the entire thesis. The conclusion of the thesis is given by briefly reviewing the key findings, the network development of ASD and TD children, in all the chapters.