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研究計畫

最佳化擴散與功能性磁振影像於人類生命週期之人腦神經與功能連結研究

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摘要

隨著認知功能和神經心理研究不斷發展，大腦的發育、成熟和衰老在其中扮演的角色逐漸受到重視，特別是其如何影響記憶、專注力或是更複雜的認知功能。近年來研究發現大腦認知功能不僅僅是來自於某特定拓譜結構上改變的影響，而是同時被複雜的大腦連結所調控。由於大腦功能由神經結構所定義，大腦結構上的神經突觸及神經元的連結分布與大腦功能的關聯亦見重要。為了解這些大腦功能網路在健康成人或疾病患者中如何調變這些複雜認知功能及行為表現，針對不同年齡層的大腦連結發展過程進行研究是重要且必須的。近年在結構性及功能性大腦連接的技術研究開啟了新的大規模腦網路概念。大腦功能以及神經心理學上的行為表現與大腦拓譜網路的關聯性在人類生命週期中發展上的改變已被提出。藉由新穎的非侵襲式磁振造影技術，人類生命週期的大腦網路的研究能夠幫助了解大腦結構性及功能性網路組織結構與行為的互動。

根據我們過去的研究成果以及可預見的未來趨勢，行為改變及大腦連結變化與年齡的相關性研究將會越趨重要。本計劃的目標是要先建立人類大腦可信的神經網路重建技術，並且將結構性與功能性網路進行屬性評估及網路整合，有助於了解生命週期大腦功能以及網路變化。在計畫的後期，為了解華人腦網路連結在生命週期中認知行為與大腦神經及功能網路結構的變化，本研究將進行成人、中老年至老年群族的認知行為與大腦神經連結分析。

本研究將進行以下階段完成上述目標：(i)最佳化大腦連結，發展具有高效及可信賴的技術重建大腦結構網絡連結；(ii)建立大腦結構性與功能性網路並進行整合；(iii, iv)發展生命週期針對成人至老年人群族的臨床行為與認知表徵與大腦連結網路做連結，希望能針對不同生命週期來進一步瞭解神經網絡的結構及功能，並應用相關技術與知識於神經科學、精神科學及病理研究。透過大腦連結的結構與功能特性，顯示大腦結構與功能連結的發展變化與認知能力的相關性，並預測大腦在生命週期的退化曲線，並於計畫結束後，與科技部合作提供兩岸之影像資料庫作為華人相關發育與老化與認知神經科學及臨床研究基礎。

關鍵詞： 老化、生命週期、大腦網路、認知退化、擴散磁振造影、功能性磁振造影

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1. Specific Aims

Accumulating evidence suggests that human brain areas do not act as independent processors but operate coherently by large-scale brain organization for specific complex cognitive functions. Anatomical linkage of synapses and associated neurons supplies the basic architecture of brain functions that are of interest to neuroscientists since connectivity patterns define functional networks. Knowledge structural connections between functional brain areas are of critical importance in the understanding of normal brain functions as well as brain abnormalities. Recent advances in the study of structural and functional brain connectivity inspire new conceptualizations of large-scale brain networks. The dynamic behaviors, including intelligence, attention, memory, social behavior, and cognitive deviations have been linked to the topology of the brain networks, which changes over the lifespan following a specific anatomic sequence. With the aids of novel in-vivo MRI techniques, a thorough knowledge of brain network across lifespan in the living human shed light on an integrated understanding of the interplay of structural and functional brain organization and behaviors.

According to our previous works and the foreseeable importance of the age-related behavior and brain connections associations, the goal of this project is to develop robust imaging methods to understand the behavior linked functional dynamics and the underlying anatomical connections across lifespan in the living human brain, especially the degeneration in advanced age. To attain the goal, structural and functional imaging methods for brain connections will be refined and optimized in the first two years. Behavior linked functional dynamics and the underlying anatomical connections in the living human brain across childhood-adulthood (3^{rd} year) and adulthood to ageing (4^{th} year) will be studied. Furthermore, our previous dataset in autism spectrum disorders (ASD) and Alzheimer's disease (AD) will be revisited according to the optimized analysis packages and database of healthy subjects. We plan to attain this goal in four chronological phases involving:

(i) Phase #1 - Development of robust and reliable diffusion MRI technologies to construct structural connections;
(ii) Phase #2 - Topological patterns of human brain structural and functional networks;
(iii) Phase #3 - Behavior linked brain connectivity change from adolescent to early adulthood;
(iv) Phase #4 - Behavior linked brain connectivity change during advanced adulthood.

With these efforts, we anticipate to optimize imaging methods in reconstruct brain networks, especially for most of the previous DTI dataset that was already acquired in various brain centers, and to construct the topological patterns of large-scale brain networks across lifespan for the behavior linked developing process of brain organization which may be applied to predict the maturing of particular cognitive functions and to predict years until psychopathic symptom onset in high-risk subjects.

2. Background and significance

Brain development, maturation and senescence are a complex process linked with widespread changes that underlies sophisticated cognitive functions and neuropsychological behaviors, including

memory, attention, and cognitive control (Crone et al., 2009). These functions are implemented through integrations and interactions within and between large-scale brain connectivity (Mesulam, 1998). The connectivity pattern is formed by structural links of synapses and associated fiber pathways and the underlying causal relationships measured as cross-correlations or coherence. Neural activity, and by extension neural codes, are constrained by the connectivity, which changes over the lifespan following a specific anatomic sequence. To understand the extensive cognitive and behavioral advances in both healthy and disease states, study of brain connectivity from childhood to aging is crucial and necessary.

For decades, neuroscientists exhibited little interest in the connections due to the limit of non-invasive technique. Although invasive studies have produced a large body of evidence concerning connectivity patterns in non-human animals (Scannell et al., 1999), direct information concerning brain connections in humans is very limited. Knowledge of the longer-distance connectivity of the human cerebral cortex is especially sparse (Young et al., 1995), which is a serious handicap for the understanding of brain function. Though the longer distance connectivity can be investigated by dissection of major tracts or histological studies of remote degeneration following a focal lesion (Van Buren & Burke, 1972), such work is based on a relatively small number of informative patients. During the past ten years, several cutting-edge imaging technologies have emerged that can acquire functional and structural connectivity data from human brains, in vivo (Sporns et al., 2005). Functional connectivity, temporal correlation of a neurophysiological index measured in different brain areas, can be obtained from the measurement of brain metabolic activity using PET (Friston et al., 1993), correlation of electrical activity within and between brain regions using EEG (Micheloyannis et al., 2006) or MEG (Stam et al., 2004), and correlation of low frequency fluctuations in the resting state detected by functional MRI (fMRI) (Biswal et al., 1995). Structural connections, neural tracts connected between brain regions, can be inferred by estimating and connecting the orientation of fiber bundles in white matter (WM) based on anisotropies in water diffusion detected by diffusion MRI (Basser et al., 1994; Mori et al., 1999). More recently, studies of human brain function in health and illness have increasingly realized the importance of connectivity data to unravel the mystery of the mind (Li et al., 2009). Plenty of reports note that many of the most common mental illnesses, from autism to schizophrenia, seem to be diseases of “faulty wiring”, in which the brain has a set of aberrant connections (Bozzali et al., 2011).

Notably, because brain connectivity is a major organizing principle of the nervous system and is fundamental to understanding brain function and dysfunction, filling this knowledge gap in knowledge is paramount. NIH therefore announces a five-year, 30 million USD, Human Connectome Project (HCP) to develop and share knowledge about the structural and functional connectivity of the human brain in 2009. Under this initiative, “connectivity” is defined at the level showing structural and/or functional linkages from one major subdivision (cortical areas or subcortical nuclei) of the brain to others. It is recognized that many current technologies are best suited to collect data from cerebral cortex, though, to the extent that it is possible, subcortical connectomic data are also of great interest to the Project. In December 2009, the ICT/Future and Emerging Technologies (FET open) of the EU FP7 funded another European consortium project to link the micron level to the whole brain.

Human MRI using voxel-wise analysis suggests an inverted U pattern with protracted growth extending into the fifth or sixth decade with subsequent accelerating decrease, indicating that at some point cerebral maturation is overtaken by effects of cerebral aging (Sowell et al., 2003; Kochunov et al., 2011). These age trajectories are regionally heterochronic, proceeding largely in the phylogenetic order and coupling with various cognitive maturations. Linkage between structural connection changes and cognitive decline in aging (Kennedy & Raz, 2009) and degenerative disease (Head et al., 2004) has also been established, conjunctively referred to as the disconnection hypothesis (Bartzokis et al., 2004). Recently, using graph theoretical approach, topological patterns and network properties of brain connections were identified and correspond with specific biological characteristics such as development (Hagmann et al., 2010), and aging (Gong et al., 2009). Hagmann et al. (2010) demonstrated that the nodal strength and efficiency increase, and the clustering coefficient decreased with age in WM networks of the late developing brain (age range: 2–18 years). Gong et al. (2009) found the negative age effect on nodal efficiency was mainly localized to regions in the parietal and occipital cortex, whereas the positive age effect concentrated on regions in the frontal and temporal cortex. Wen et al. (2011), exploiting the association between cognitive functions and the attributes of structural brain networks from 342 healthy elders (age range: 72–92 years), showed that the processing speed, visuospatial, and executive functions are associated with the global efficiency of structural brain networks, and that many regions (59 regions out of 68) including most of the frontal and temporal cortices, have decreased nodal efficiency with age. Moreover, this work identified that, for the first time, regional anatomical connectivity maps relate to processing speed and visuospatial and executive functions in the elders. Given that the mature human brain has structurally been optimally organized into a complex network, studying the topological patterns of large-scale brain networks in a global level across a lifespan may provide more intellections for the developing process of brain organization (Lo et al., 2011). Notably, prediction of individual maturation was recent reported by the weakening of short-range functional connectivity between the adult brain's major functional networks from the dynamic functional connectivity (Dosenbach et al., 2010). The results suggested that the functional connectivity approach derives its accuracy from important neurophysiologic changes and shed some light in predicting the maturing of particular cognitive functions. Importantly, it also provides a way to predict years until psychopathic symptom onset in high-risk subjects or to prognosticate treatment effect of neuropsychiatric disorders.

Plenty studies have shown age-related cognitive performance. Working memory, the ability to hold information in memory for short time periods for use in complex tasks (Baddeley et al., 1998), continues to develop throughout adolescence (Conklin et al., 2007). Development of the cortical regions in the fronto-parietal network has been characterized by functional and diffusion MRI throughout late childhood and adolescence. Increase in working memory capacity as seen during childhood and adolescence, was linked to the late cortical maturation of the frontal lobes, and to the development of the pathways connecting these areas (Finn et al., 2010). Other cognitive functions include the maturation of spoken word-processing of Mandarin Chinese (Cao et al., 2011), reading competence (Koyama et al., 2011), and attention (Chu-Shore et al., 2011), have also been reported to involve in the development of brain networks. Our results have indicated age-related social and analytic brain development and aberrant neurodevelopment in autism (Wen et al., 2011). Aging is also related to a decline in information-processing resources, such as working memory capacity, attention regulation and processing

speed, and this change is likely to be related to brain structural changes (Burns et al., 2005). A recent study (Seeley et al., 2009) has shown strong convergence between intrinsic functional connectivity and structural covariance, with functional network maps closely mirroring cortical atrophy patterns in five neurodegenerative syndromes and attributed the late-life cognitive declines as disconnection syndrome (Carmichael & Lockhart, 2011). Coordinated activity of distributed sets of brain regions is required for successful higher-order thought but may gradually degenerated in late-life period.

During the past decade, our research efforts focus the technologies for structural connection and the applications to neuroscience and brain illness. We noticed that brain connectivity is close coupling with the cognitive functions, not only behavioral deviation or dysfunction but also personal variations in cognitive behaviors such as memory, social and analytic ability, and language performance. Understanding neural connectivity in model organisms has made possible an integrated understanding of the interplay of genes, molecules, cells, neural systems, and behavior. Meanwhile, we pay heed to the complex process of brain development, maturation and senescence as it close linked with behavioral, cognitive and overall progress throughout childhood, adolescence, adulthood and into ageing. A thorough knowledge and database of structural and functional brain connectivity across lifespan and age-related behaviors association is crucial and necessary for understanding the extensive cognitive and behavioral advances in both healthy and disease states, however, is still uncompleted.

According to our previous works and the foreseeable importance of brain connections, the goal of this project is to develop robust imaging methods to understand the behavior linked functional dynamics and the underlying anatomical connections across lifespan in the living human brain. In the first two years, structural and functional imaging methods for brain connections will be refined and optimized. The current methods for assessing structural and functional connectivity have shown their promise and potential, however, there are several technical limitations at multiple levels. Despite HARDI has shown its potential in determine crossing fibers, demand of long acquisition time still retards the usage of in clinical or routine studies (Cho et al., 2009). Analyses of structural connectivity must cope with a high incidence of false positives and false negatives, combined with an inherent difficulty in making quantitative estimates of connection strength (Jones & Cercignani, 2010). In addition, functional correlations reflect more than direct anatomical connectivity (Vincent et al., 2007), as they can be influenced by common inputs and/or interactions via serially connected areas. Consequently, effect to further large-scale brain networks using graph theoretical approach and the associations to functional connectivity is uncertain.

Therefore, in the first year, we propose to apply new reconstruction algorithm, constrained spherical deconvolution (CSD), to resolve crossing fibers from DTI dataset. CSD has shown its ability to resolve crossing fibers from HARDI dataset in b value of 2,000 s/mm2 in our previous study (Tournier et al., 2008). Our preliminary result shows this method has potential to resolve multifiber orientations from our previous DTI dataset which was acquired from clinical 1.5T MRI. By comparing with conventional DTI and HARDI methods, phantom model and human data will be applied to evaluate the accuracy of this new method in DTI dataset. Meanwhile, various neural tractography algorithms will be applied in 20 subjects, who will be recruited for two MR scans, to assess the stability of structural connections.

In the second year, effect of this new method to further large-scale brain networks using graph theoretical approach will be evaluated and compared with our previous results (Baddeley et al., 1998; Bullmore & Sporns, 2009). Reliability of the brain networks, especially in long-rang connections, will be evaluated. Based on these results, topological patterns of human brain structural and functional networks will be integrated. Meanwhile, structural connections constrained functional causality analysis will be implemented to improve models of functional integration.

In the last two years, behavior linked functional dynamics and the underlying anatomical connections in the living human brain across childhood-adulthood (3rd year) and adulthood to aging (4th year) will be studied. Integrated with our previous aging (100 male subjects, 60 y/o – 85 y/o) and adulthood (60 males and 60 females, 20 y/o – 59 y/o) dataset, we aim to recruit another 300 subjects from 10 y/o to 85 y/o in the coming 4 years to have a complete view of the functional dynamics and the underlying anatomical connections across lifespan. Neuropsychological tests, including working memory, attention and intelligent evaluation, will be associated with age-related change of brain networks. From these dataset, prediction of individual maturation in particular cognitive function will be studied. Meanwhile, our previous dataset in autism spectrum disorders (ASD) and Alzheimer's disease (AD) will be revisited according to the optimized analysis packages and the typical topological patterns from healthy subjects.

With these efforts, we anticipate to optimize imaging methods in reconstruct brain networks, especially for most of the previous DTI dataset that was already acquired in various brain centers, and to construct the topological patterns of large-scale brain networks across lifespan for the behavior linked developing process of brain organization which may be applied to predict the maturing of particular cognitive functions and to predict years until psychopathic symptom onset in high-risk subjects.

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Mapping brain connections change across the human lifespan with optimum diffusion and functional MRI

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Abstract

Brain development, maturation and senescence are a complex process linked with widespread change that underlies sophisticated cognitive functions and neuropsychological behaviors including memory, attention, and cognitive control. Growing evidence shows that human brain function is not only modulated by brain topological changes but also operates coherently by large-scale brain organization for specific complex cognitive functions. Anatomical linkage of synapses and associated neurons supplies the basic architecture of brain functions that are of interest to neuroscientists since connectivity patterns define functional networks. To understand the extensive cognitive and behavioral advances in both healthy and disease states, study of brain connectivity from childhood to aging is crucial and necessary.

Recent advances in the study of structural and functional brain connectivity inspire new conceptualizations of large-scale brain networks. The dynamic and neuropsychological behaviors have been demonstrated to link the topology of the brain networks, which changes over the lifespan etiology following a specific anatomical sequence. With the aid of novel in-vivo MRI techniques, a thorough knowledge of brain network across the lifespan in living humans sheds light on an integrated understanding of the interplay of structural and functional brain organization and behavior.

Based on our previous work and the foreseeable importance of age-related behavior and brain connection associations, the goal of this project is to develop a robust reconstruction algorithm for structural connectivity to build reliable brain connectivity models in living human brains, or human connectomics (neuroconnectomics). Sequentially, the properties of structural and functional networks will be examined and further integrated to improve the models of functional integration. It will allow us to study brain connections and functional integration across the lifespan in a large-scale brain network. In the last two years, to elucidate a complete view of the functional dynamics and the underlying anatomical connections across the lifespan, behavior-linked functional dynamics and the underlying anatomical connections in the living human brain across childhood-adulthood (3rd year) and adulthood to ageing (4th year) will be studied.

In order to achieve this goal, we anticipate to (i) optimize imaging methods in reconstructed brain networks, especially for most of the previous DTI dataset that was already acquired in various global brain enters, and to (ii) construct the topological patterns of large-scale brain networks across the lifespan for the (iii, iv) behavior-linked developing process of brain organization during early adulthood and in older adults, which may be applied to predict the maturing of particular cognitive functions and to predict years until neurodegenerative symptom onset in high-risk subjects. With these efforts, we can reveal the

development of brain structural and functional connectivity underlying alterations in cognitive abilities and predict individual brain maturity through the lifespan. At the end of this project, the database will be released for international academic research, under the agreement from Taiwan's Ministry of Science and Technology. This project should prove helpful to further aging/development studies in brain functions and disorders, and inform evidence-based robust clinical interventions.

Keywords: aging, lifespan, brain network, cognitive decline, diffusion MRI, functional MRI