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醫學院國際醫學研究碩博士學位學程Paola Magioncalda老師學術分享：精神疾病的精神病理學和病理生理學

我的學術教育和研究經驗為本人提供精神病學和神經科學的背景，從義大利熱那亞大學醫學院畢業並專攻精神病學後，獲得荷蘭馬城大學研究型情感神經科學碩士學位和義大利熱那亞大學神經科學博士學位。我先擔任研究員，在熱那亞大學神經科學系進行研究工作，還在多個國際研究中心擔任客座研究員，進行數期培訓和研究工作，包括加拿大渥太華大學心腦成像和神經倫理學中心、美國紐約西奈山伊坎醫學院、臺北醫學大學大腦與意識研究中心，和中國成都四川大學心理健康中心與精神病學實驗室。

2019 年底，我開始在北醫大雙和醫院擔任醫學研究員，最後我加入臺北醫學大學，擔任醫學院國際醫學研究碩博士學位學程（IGPM）助理教授和心智意識與腦科學研究所（GIMBC）的合聘助理教授。我在本校建立了「精神神經科學研究室」，並與心智意識與腦科學研究所的 Matteo Martino 博士一起經營，持續發展研究工作。

我的長期研究聚焦在了解大腦現象體驗活動與行為之間的關係，以及研究主要精神疾病（尤其是躁鬱症）的精神病理學和病理生理學。這些研究領域在精神神經科學中是互補的，因為更深入地了解大腦生理學是研究大腦變化的基礎，而對精神疾病的神經生物學之研究，可能對大腦運作更全面性的了解，並提供有價值的見解。在這方面，躁鬱症可能具有特別的相關性，躁鬱症是一種主要的精神疾病，其特徵是躁狂和抑鬱狀態，在各種精神病理學領域表現出相反的改變模式，包括心理動作、情感和思維，因此，躁鬱症可以代表一個獨特的模型來研究現象和行為模式的變化與大腦運作變化的相關性，另一方面，對精神疾病（如躁鬱症）的病理生理學的機制理解，是對這些嚴重又讓人衰弱的疾病實施特定診斷工具和有效治療的關鍵步驟。【左圖：醫學院國際醫學研究碩博士學位學程 Paola Magioncalda 助理教授】

過去幾年，在與 Matteo Martino 博士的密切合作下，我運用各種神經影像學和實驗室技術進行一系列研究，以查證躁鬱症潛在的神經生物學改變，研究顯示躁症和鬱症與內在大腦活動的功能結構明顯變化有關，這種內在的大腦活動代表大腦自發性地產生神經元活動，並設定從環境輸入和輸出的基線處理；研究發現，大腦內部活動功能重構發生於躁鬱症，與躁症和鬱症大規模的腦部網絡間存在著相反的失衡，這導致內在大腦活動對環境的相對過度調整或失調，最終表現在與躁狂和抑鬱症狀相關的反向現象行為改變，進一步的結果顯示，這種網絡失衡與皮層下皮質的耦合和神經傳導物質信號傳導的明顯變化有關，最後，我們檢測到大腦白質異常與躁鬱症患者的免疫炎症改變相關。【右圖：Paola Magioncalda 老師（右 4）與研究團隊合影】

根據這些數據，我們最近提出躁鬱症病理生理學的理論模型，旨在將免疫炎症狀態的變化、白質損傷、大腦內部活動的變化和精神病理學連結起來，簡而言之，模型顯示躁鬱症的核心病理生理機制可追溯到免疫/炎症介導的白質損傷，涉及使神經遞質信號不穩定的邊緣束，並且這種神經遞質信號的變化，導致內在大腦活動的階段性重構，而大腦網絡之間的失衡，臨床表現為躁鬱症症狀學。

目前，在臺北醫學大學和國家科學及技術委員會各種補助金資助，我們正積極進行一個項目，來檢驗從躁鬱症病理生理學理論模型中出現的特定假設，此外，基於該模型，我們計劃使用動物模型進行研究，以從機制上了解免疫介導的白質損傷在躁鬱症中的作用，並測試保護和修復白質的潛在療法，這些研究的數據可以對精神醫學神經科學做出相關貢獻，並可能為躁鬱症和其他神經精神疾病提供創新、有效和以神經科學為基礎的治療方法。（文/Paola Magioncalda，醫學院國際醫學研究碩博士學位學程助理教授）

【下圖：Paola Magioncalda 老師（左 2）、Matteo Martino 老師（左 1）與研究團隊合影】

My academic training and research experience have provided me with a background in psychiatry and neuroscience. After graduating from medical school and specializing in Psychiatry (University of Genoa, Italy), I obtained a postgraduate research Master's degree in Affective Neuroscience (Maastricht University, Netherlands) and a Ph.D. degree in Neuroscience (University of Genoa, Italy). Firstly, as a research fellow, I conducted my research work at the Department of Neuroscience of the University of Genoa (Italy). I also spent several periods of training and research work at various international research centers as visiting researcher, including the Mind Brain Imaging and Neuroethics Center (University of Ottawa, Canada), Icahn School of Medicine at Mount Sinai (New York, U.S.), Research Center for Brain and Consciousness (Taipei Medical University, Taiwan), and Mental Health Centre and Psychiatric Laboratory (Sichuan University, Chengdu, China).

At the end of 2019, I started working as a medical researcher at Taipei Medical University – Shuang Ho Hospital. Finally, I joined Taipei Medical University as an assistant professor of the International Master/Ph.D. Program in Medicine (IGPM) of the College of Medicine and as a joint-appointment assistant professor of the Graduate Institute of Mind Brain and Consciousness (GIMBC).At Taipei Medical University, I had the opportunity to build my Lab, the Psychiatric Neuroscience Lab, which I am running with Dr. Matteo Martino (a TMU assistant professor of GIMBC), and continue developing my research work.

My long-term research interest is focused on understanding the relationship of brain functioning with phenomenal experience and behavior, as well as investigating the psychopathology and pathophysiology of major psychiatric disorders, especially bipolar disorder. These research areas are complementary in psychiatric neuroscience since a better understanding of brain physiology is fundamental for the study of brain alterations, while the investigation of the neurobiology of psychiatric disorders may provide valuable insights for a better comprehension of how the brain works. In this regard, bipolar disorder can be of particular relevance. Bipolar disorder is a major psychiatric disorder characterized by manic and depressive states that show opposite patterns of alterations across various psychopathological domains, including psychomotricity, affectivity, and thought. Thus, bipolar disorder can represent a unique

model to investigate how changes in phenomenal and behavioral patterns are related to changes in brain functioning. On the other hand, a mechanistic understanding of the pathophysiology of psychiatric disorders, such as bipolar disorder, represents a crucial step for implementing specific diagnostic tools and effective therapies for these severe and debilitating illnesses.

In the last years, in strict collaboration with Dr. Matteo Martino, I conducted a series of research studies to investigate the potential neurobiological alterations underlying bipolar disorder, using various neuroimaging and laboratory techniques. Our research showed that mania and depression are related to distinct changes in the functional architecture of intrinsic brain activity. Such intrinsic brain activity represents the neuronal activity spontaneously produced by the brain and sets the baseline processing of inputs and outputs from and to the environment. Our findings suggested that a functional reconfiguration of intrinsic brain activity occurs in bipolar disorder with an opposite dysbalance between large-scale brain networks in mania and depression, which results in a relative over-tuning or de-tuning of intrinsic brain activity to the environment, finally manifesting in the opposite phenomenal-behavioral changes associated with manic and depressive symptomatology. Further results showed that such network dysbalance is associated with distinct changes in the subcortical-cortical coupling and neurotransmitter signaling. Finally, we detected abnormalities in the brain's white matter that correlated with immune-inflammatory alterations in patients with bipolar disorder.

Based on these data, we recently proposed a theoretical model of the pathophysiology of bipolar disorder aimed at linking changes in the immune-inflammatory status, damage of white matter, alterations in intrinsic brain activity, and psychopathology. Briefly, our model suggests that the core pathophysiological mechanism of bipolar disorder is traceable to immune/inflammatory-mediated damage of white matter involving the limbic tracts that destabilize the neurotransmitter signaling, and changes in such neurotransmitter signaling lead to phasic reconfigurations of intrinsic brain activity, resulting in a dysbalance between brain networks that clinically manifests in the manic-depressive symptomatology.

We are now conducting an ambitious project (funded by various TMU and NSTC grants) to test the specific hypotheses that emerged from our theoretical model of the pathophysiology of bipolar disorder. Moreover, based on this model, we are planning to implement studies using animal models to obtain a mechanistic understanding of the role of immune-mediated damage of white matter in bipolar disorder, as well as to test potential therapies to protect and repair the white matter. Data from these studies can make a relevant contribution to psychiatric neuroscience and potentially provide an innovative, effective, and neuroscientific-based treatment for bipolar disorder and other neuropsychiatric disorders.