Determining pathways that link brain, body, lifestyle and mental health

Using multimodal brain imaging and organ-specific physiological markers from more than 18,000 adult participants of the UK Biobank database, this study reveals integrated pathways that explain the interplay between brain, body, environment and lifestyle, and their collective influence on mental health outcomes.

This is a summary of:
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The mission

Depression and anxiety are common mental health conditions. As well as being highly comorbid with each other[1], the prevalence of depression and anxiety is also high in individuals with a chronic physical health condition, such as coronary heart disease, respiratory disease and diabetes mellitus[2,3]. Several putative biological and psychosocial pathways have been proposed to attempt to explain the link between physical and mental health conditions. Notably, the brain is rarely considered in these models; however, depression and anxiety are commonly associated with alterations in brain structure and function[4]. Further work is therefore needed to understand the role of the brain on the concurrent manifestations of physical and mental illness. This knowledge could help to reduce the mental–physical dichotomy in medicine and facilitate integrated and holistic health care across psychiatry and other medical disciplines.

The discovery

We analyzed multimodal brain MRI, physiological markers, and blood-derived and urine-derived markers from 18,128 adult (age range 40–70 years) participants of the UK Biobank database. Physical health was assessed for each body organ system (that is, cardiovascular, pulmonary, musculoskeletal, immune, renal, hepatic and metabolic) using organ-specific phenotypes. Brain imaging acquired at 4–14 years of follow-up was used to assess brain health. Subsequently, normative models were used to assess the extent to which each individual's organ health and function deviated from age-specific and sex-specific normative references ranges. Finally, structural equation modeling (path analysis) was used to test the importance of pathways from physical health to mental health via structural alterations in brain gray and white matter.

Several pathways were discovered through which poor organ health could influence brain health, which in turn could lead to worsened mental health. For example, poor musculoskeletal and immune health was associated with reductions in the volume of brain gray matter, which can contribute to depressive symptoms (Fig. 1a). Several lifestyle and environmental factors were also identified that influenced mental health via their selective effects on the physiology of specific organ systems and brain structure. Notably, physical activity, sedentary behavior, diet, sleep quality, education and socioeconomic inequality influenced mental health by modulating several body and brain systems. For example, smoking had a specific pathway that affected mental health by metabolic (Fig.1b) and pulmonary systems.

The implications

This study provides an integrated model that links physical health, neurobiology and mental health outcomes. The findings suggest a crucial role of the brain in mediating the relationship between physical and mental health, which is an important step toward bridging the dualism of mind and body. Importantly, modifiable lifestyle factors were identified that could potentially inform the development of targeted interventions to improve both physical and mental health synergistically.

Of note, this study has several limitations. First, brain imaging and mental health assessments were not available during the first study phase of the UK Biobank, when physical health was assessed. Thus, we were unable to assess whether the individual variation in brain structure and severity of mental health symptoms observed at follow-up was consistent with longitudinal alterations in brain structure and mental health status, consequent to physical health changes. Second, owing to the sequential and non-randomized assessment of participants, we were unable to assess pathways in which poor mental health leads to poor physical health via effects on brain structure, or by which alterations in brain structure might lead to poor mental health via effects on physical health, or by which impaired physical health could lead to reduced lifestyle activities, which in turn influences brain and mental health.

The study focuses on characterizing neurobiological influences on physical and mental health from a macroscale perspective. Future studies using alternative neuroimaging techniques (such as positron emission tomography of neurotransmitters, magnetic resonance spectroscopy of cerebral metabolites, and free water imaging of neuroinflammation) would complement the MRI-derived phenotypes used here and provide insight into the underlying molecular pathways. Moreover, further work is needed to determine whether interventions informed by the pathways identified here would lead to improved physical and mental health outcomes and reduce the risk and adverse effects of physical–mental comorbidity.

Ye Ella Tian
The University of Melbourne, Parkville, Australia.

EXPERT OPINION

"This is a very important study linking physical and mental health and the role of brain structure and lifestyle factors. The study is well designed, and the large number of participants offers a unique way of understanding the relationship between the brain and physical health. Another major strength of the study is that it takes into account lifestyle factors that might contribute to this relationship." **Bruno Agustini, Deakin University, Geelong, Australia.**

FIGURE

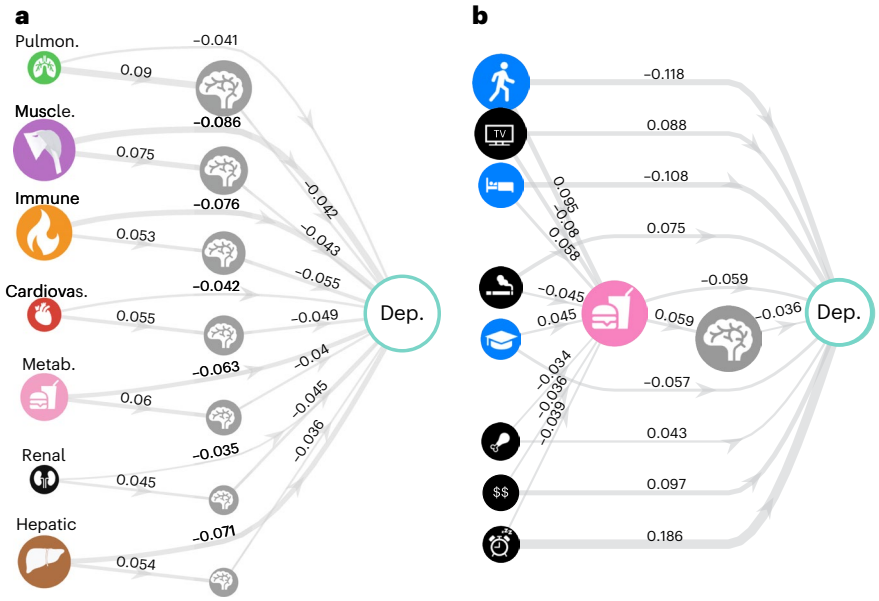

Fig. 1 | Pathways linking brain, body, lifestyle and depression. a, A structural equation model (SEM) links the health of each organ system to severity of depression, with gray matter volume as the mediating factor. Poor health of organs leads to a reduction in brain gray matter and subsequent depressive symptoms. **b**, A SEM was used to show that lifestyle factors (indicated by icons) influence depressive symptoms via effects on metabolic health. In both panels, edge thickness reflects regression coefficients estimated for edges comprising the SEM. Cardiovas., cardiovascular; dep., depression; metab., metabolic; muscle., musculoskeletal; pulmon., pulmonary. © 2024, Tian, Y. E. et al.

BEHIND THE PAPER

The research idea was inspired from our 'usual' tearoom discussion around causes versus consequences. We considered whether the changes in brain structure and function that we observed in MRI scans are the causes or the consequences of mental illnesses. Later, the discussion went beyond the neural-centric view of mental illness, which is backed by one of our recent studies[5] in which we show that poor body health is a more pronounced manifestation of mental illness than poor brain health. Despite the unequivocal neural basis of mental illness, we are convinced that it is important to also consider the dynamic and interactive nature between the brain, body, mental health and lifestyle and environmental factors. This research direction is intriguing and exciting because it enables a holistic view of physical and mental health, which could facilitate integrated and holistic health care across psychiatry and other medical disciplines. **Y.E.T.**

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FROM THE EDITOR

"Mental health research is increasingly considering the brain–body connection. This study exemplifies how large cohort datasets such as the UK Biobank allow us to capture complex and poorly understood relationships by giving us access to how factors such as physiology, lifestyle and brain structure conjointly contribute to mental health outcomes." **Rebecca Cooney, Chief Editor, *Nature Mental Health*.**