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LETTER

The Innovation Medicine

Beyond joints inflammation: The hidden neurological and psychiatric burden of rheumatoid arthritis

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Received: November 20, 2024; Accepted: February 13, 2025; Published Online: February 17, 2025; https://doi.org/10.59717/j.xinn-med.2025.100114

Citation: Zhang Q., Lu R., Luo Y., et al. (2025). Beyond joints inflammation: The hidden neurological and psychiatric burden of rheumatoid arthritis. *The Innovation Medicine* 3:100114.

Dear Editor,

The intricate connections between the brain and extracerebral organs, such as the heart and bones, have garnered increasing recognition in the scientific community. Recent studies by Zhao et al. have unveiled structural and genetic associations between the heart and brain.[1] Extending beyond the cardio-cerebral axis, a correlation between bone and brain has been reported, reinforcing the bone-brain nexus.[2] Despite the integral role of bones in joint function, research elucidating the potential holistic connection between joints and the brain remains sparse.

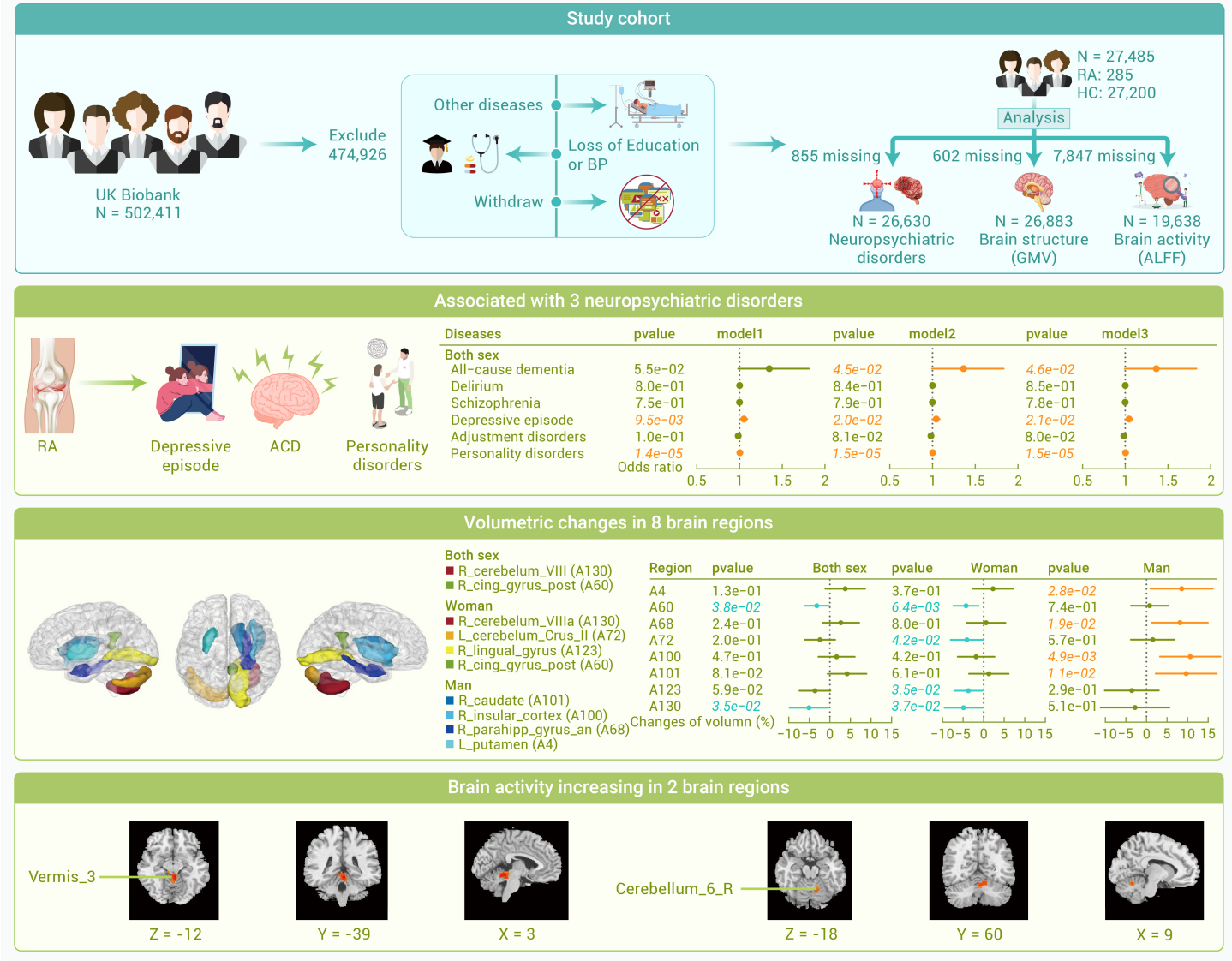

Figure 1. Overview of the study Schematic representation of the workflow used in this study. Totally 474,926 participants with basic diseases or without basic data and follow-up information were excluded from the UKB cohort (N = 502,411). Finally, 27,485 participants were chosen for further correlation research. The odds ratio of 3 kinds neuropsychiatric disorders were found increased by RA through logistic regression. Linear regression was used to discover that volumetric changes of 8 brain regions was affected by RA. It was found that the brain activity in 2 brain regions were related to RA by fMRI analysis.

Among joint pathologies, rheumatoid arthritis (RA) stands out as a distinct autoimmune disorder with documented effects on joints and a plethora of extra-articular manifestations, including cardiac, pulmonary, and renal involvement. However, the literature is scarce regarding the additional burden of RA on brain health, highlighting an urgent need for robust real-world data to substantiate this association.

To investigate the correlation between RA and brain health, we conducted an analysis leveraging neuropsychiatric disorders and neuroimaging data from the UK Biobank (UKB) cohort, comprising 502,411 participants. RA diagnosis was ascertained based on methodologies from a previous study.[3] Participants with other forms of arthritis, such as osteoarthritis, gout, psoriatic arthritis, and infectious arthritis, or those lacking follow-up information, were excluded. Ultimately, 27,485 participants were selected for further correlation analysis (Figure 1).

Logistic regression analysis revealed a significant impact of mixed-gender RA patients on all-cause dementia, depressive episodes, and personality disorders (Figure 1). Notably, RA in females was associated with an increased odds ratio for depressive episodes, while in males, RA was linked to all-cause dementia and personality disorders (see: https://github.com/Orthozq/TIME8-0123/blob/main/Efig1.pdf). To further explore the impact of gender differences on neuropsychiatric diseases, we analyzed the risk of diseases before and after menopause in women with an extra adjustment that if used hormone-replacement therapy (HRT) (see: https://github.com/Orthozq/TIME8-0123/blob/main/Efig2.pdf). Surprisingly, the odds ratio of depressive episodes became statistically insignificant in post-menopausal RA patients. More importantly, we discovered that pre-menopausal RA patients could also promote the occurrence of delirium. However, the risk of all-cause dementia and personality disorders did not change before and after menopause. These findings suggest that changes in female hormone levels may influence the neuropsychiatric damage caused by RA.

Neuroimaging analyses identified associations between RA and reduced volumes of R_cerebellum_VIIIa and R_cing_gyrus_post in mixed-gender analyses (Figure 1). Further analysis also revealed gender differences in volume changes. Females exhibited additional volume reductions in L_cerebellum_crus_II and R_lingual_gyrus, while males showed no such reductions but instead demonstrated enlargement in four brain structures: R_caudate, R_insular_cortex, R_parahippocampal_gyrus_anterior, and L_putamen. Recent research suggests that brain activity is associated with the neuropsychiatric system. However, only in RA males, we found remarkable differences with an increase in brain activity of vermis III (Anatomical Automatic Labeling, AAL: vermis_3) and the right cerebellum VI (AAL: Cerebellum_6_R) (Figure 1).

Expanding on these findings, we hypothesize that the time elapsed since rheumatoid arthritis diagnosis might correlate with the neuropsychiatric system. Correlation analysis indicated a nonlinear association between the number of days post-RA diagnosis and the A123 brain region (R_lingual_gyrus) ($p = 0.007$) (see: https://github.com/Orthozq/TIME8-0123/blob/main/Efig3.pdf). However, no significant correlations were observed in psychiatric disorders, other gray matter regions, or brain activity ($p > 0.05$).

Neuropsychiatric disorders are often accompanied by alterations in brain volume[4,5] and function.[6,7] Our results suggest that RA, irrespective of gender, leads to a reduction in gray matter volume in two brain regions, with a decrease approaching 5%. This effect was more pronounced in females, who also experienced additional gray matter volume reduction in two other regions. Interestingly, males with RA showed an opposite trend, with structural remodeling indicating increased gray matter volume. Extensive research has implicated atrophy in these regions in male RA patients with dementia risk.[8,9] Considering the observed increase in volumes, our findings suggest that males with RA are at a higher risk of developing dementia, and the changes in gray matter volume may reflect a pre-dementia compensatory state.

Resting-state functional magnetic resonance imaging (fMRI) is a critical diagnostic neuroimaging modality reflecting changes in brain activity. Our comparative study found no statistically significant differences in the amplitude of low-frequency fluctuation (ALFF) values across mixed-gender and female patients. However, male RA patients exhibited significantly increased brain activity in two cerebellum regions (vermis III and right cerebellar lobule VI) ($P < 0.05$) (Figure 1). Hypermetabolism in these regions has been reported in patients with Parkinson's disease and cognitive impairment, suggesting a link to cognitive impairment.[10] Our results, showing increased activity in vermis III and right cerebellar lobule VI, support this association.

In summary, our study reveals that RA not only increases the odds ratio of neuropsychiatric disorders but also impacts gray matter volume and brain activity. These findings underscore the importance of vigilant monitoring of the neuropsychiatric system in RA patients.

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FUNDING AND ACKNOWLEDGMENTS

We thank the UK Biobank database for the access of patients information. The project was funded by National Natural Science Foundation of China (82172387, 82372371, 82102559, 82402763), the Natural Science Foundation of Jiangsu Province (BK20230002), the Suzhou Science and Technology Development Plan (SKY2023035, SZM2023003), Gusu Health Talents Program (GSWS2022125). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

JL conceptualized and designed the study. QZ, RL, and YL performed formal analyses. YL and QZ were involved in collecting and interpreting the data on neuropsychiatric disorders. RL and QZ were involved in collecting and interpreting the neuroimaging data. RL and QZ drafted the initial manuscript. MW, ZC and RZ modified the initial manuscript and figures. JL supervised the work. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

This study was conducted using publicly available de-identified data; therefore, it did not require additional ethical approval or patient consent.

DATA AND CODE AVAILABILITY

Full individual participant data cannot be openly shared under the policy with UK Biobank and ethics approval. Further information about applying for data access can be obtained from the UKB website (https://www.ukbiobank.ac.uk). Method information is available from the corresponding author upon reasonable request, or the website (https://github.com/Orthozq/TIME8-0123/blob/main/MethodSection.pdf).