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EDITORIAL
Vascular biology and medicine

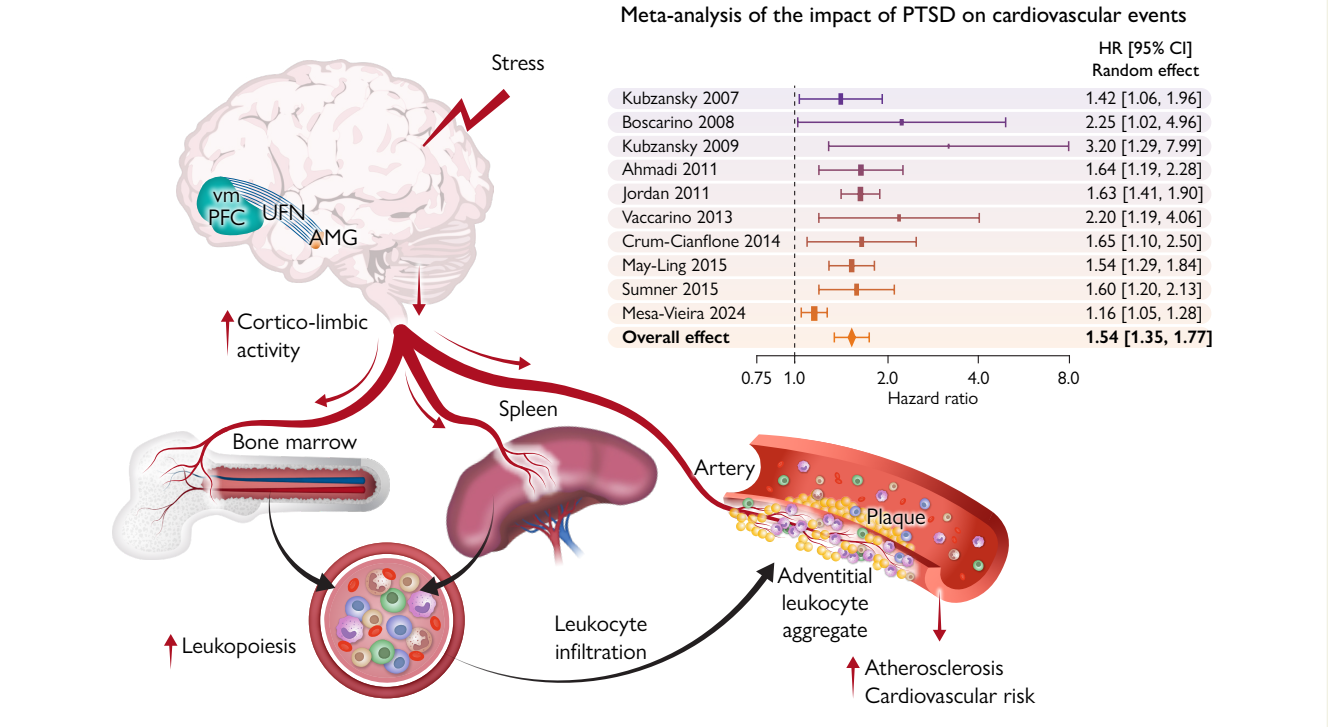
Cortico-limbic restructuring and atherosclerosis: a stressful liaison

Sarajo K. Mohanta [1,2], Donato Santovito [1,2,3], and Christian Weber [1,2,4,5]*

[1]Institute for Cardiovascular Prevention (IPEK), Ludwig-Maximilians-Universität (LMU), LMU University Hospital, Pettenkoferstr. 9, D-80336 Munich, Germany; [2]German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, Munich, Germany; [3]Institute for Genetic and Biomedical Research (IRGB), Unit of Milan, National Research Council, Milan, Italy; [4]Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands; and [5]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

This editorial refers to 'Cortico-limbic interactions and carotid atherosclerotic burden during chronic stress exposure', by C. Gharios *et al.*, https://doi.org/10.1093/eurheartj/ehae149.

Graphical Abstract



Psychological stress reshapes neurovascular brain–body interactions to affect atherosclerosis. In patients with post-traumatic stress disorder (PTSD), chronic psychological stress enhances cortico-limbic activities of the ventromedial prefrontal cortex (vmPFC) and amygdala (AMG), and decreases neural integrity of the uncinated fasciculus (UFN) connecting both structures in the orbitofrontal and lateral lobes of the cortex. This central neural restructuring may lead to enhanced peripheral leucopoiesis in the bone marrow and lymphoid tissues, and possibly leucocyte recruitment within adventitia and atherosclerotic plaques. Eventually, this neural network can underly the higher cardiovascular risk of PTSD patients observed across a wide core of the literature.

* Corresponding author. Tel: +49 89 440054530, Fax: +49 89 440054532, Email: chweber@med.lmu.de

Psychological stress and cardiovascular disease have been associated for a long time. Despite the complexity of a lack of a univocal definition or measurement, epidemiological studies performed 20 years ago revealed that stress constitutes an attributable risk for cardiovascular events comparable with conventional risk factors.[1–3] On the one hand, acute mental stress has been more commonly associated with cardiovascular events and linked to the activation of acute stress response mechanisms (i.e. hypothalamic–pituitary–adrenal axis and sympathetic nervous system outputs) precipitating atherosclerotic plaque vulnerability.[4] On the other hand, the relationship between chronic stress and the development of atherosclerosis and cardiovascular disease appears more complex. A *prima vista* hypothesis may postulate that stress has detrimental effects on cardiovascular health via a maladaptive lifestyle or socioeconomically contingent conditions. However, the effect of stress is independent of age, geographic region, sex, socioeconomic status, and smoking status.[3] Other mechanisms have been shown to be involved, such as the activation of neural circuits involved in the perception of fear (i.e. the amygdala and other higher order brain areas) with their influence on bone marrow leucocyte production and mobilization.[5,6] However, understanding of the complex wiring between the brain and the cardiovascular system and its relevance for cardiovascular pathophysiology is far from being complete.

A historical rationale for why the neuro-vascular connection has been neglected for years is the assumption that the vessel wall of large- and medium-sized arteries lacks extrinsic innervation. However, Andreas Vesalius, the father of modern anatomy, reported the close proximity between blood vessels and the peripheral nerves already in his book *De Humani Corporis Fabrica* as early as the 16th century.[7] Yet recent evidence has profoundly changed the view on neuro-vascular cross-talk, raising awareness of the existence and relevance of physical and functional interactions between the cardiovascular system and the nervous system. Indeed, multiple interfaces connecting the cardiovascular, immune, and nervous systems in advanced atherosclerosis have recently been identified.[8–10] These multisystemic trilateral interactions form neuroimmune cardiovascular interfaces and cardiovascular–brain circuits involved in central (brain) and peripheral (body) processes to regulate behavioural states including emotions, empathy, and stress that affect cardiovascular responses.[6,7,11] Notably, adventitial neuroimmune cardiovascular interfaces show robust neural restructuring of peripheral nerves originating from perivascular ganglia that may trigger the formation of adventitia leucocyte aggregates adjacent to atherosclerotic plaques in diseased arteries and employ afferent and efferent paravascular ganglia to form multisynaptic artery brain connections with higher order brain areas including the brainstem, amygdala, and hypothalamus to regulate atherosclerosis. Moreover, evidence shows how atherosclerosis affects the activities of distinct brain areas including the amygdala of hyperlipidaemic mice[8] and how hypertension alters the structural integrity of specific white matter structures including the uncinate fasciculus in hypertensive patients.[12]

In this issue of the *European Heart Journal*, Gharios *et al.* aim to extend to humans the knowledge of the complex network between the brain and the cardiovascular system to shed light on the relationship between neural networks affected by chronic stress and vascular disease.[13] By multimodal imaging approaches, the authors have investigated the brain, assessing the activity of stress-associated networks and the axonal integrity of cortico-limbic circuits, and arteries, by concomitant determination of vascular plaque burden, as well as bone marrow and lymphoid organs. As a clinical model, the authors focused on patients with a diagnosis of post-traumatic stress disorder (PTSD), as a well-established condition of chronic psychological stress with an established association with cardiovascular disease.[14,15] Patients affected by PTSD had higher activation of the stress-associated neural networks and reduced integrity of the uncinate fasciculus axons (especially in the left hemisphere), and both parameters correlated with carotid atherosclerosis burden after adjustment for classical cardiovascular risk factors. Similar results were obtained for the ascending aorta, although these did not reach statistical significance. These findings extend and further integrate previous work from the authors, showing that the activity of the amygdala is an independent predictor of cardiovascular events in a longitudinal cohort reflecting the general population.[5] Yet, the present study highlights the importance of a more extensive investigation of neural networks, rather than a limited focus on the limbic system or the amygdala. Indeed, an important finding of the study is that axonal integrity of the uncinate fasciculus, an intercerebral white matter fibre tract connecting the amygdala and the limbic system with the orbitofrontal cortex, is inversely associated with the stress-associated neural network activity and with the carotid atherosclerotic burden. This discovery might lead to new views on the relevance of the frontal cortex in the control of the limbic system and its influence on cardiovascular health in humans. Yet, replications of these findings in larger prospective cohorts and detailed optogenetic investigations in animal models are warranted to dissect the neural networks involved.

An aspect that the study by Gharios *et al.* could not clarify is the underlying mechanism(s) of the observed associations between stress-associated neural activity and subclinical atherosclerosis. While a higher plasma high-sensitivity C-reactive protein (hsCRP) concentration was detected in patients with PTSD which positively correlated with stress-associated neural activity (but only on the left hemisphere) and carotid atherosclerosis, no significant associations were found with vascular inflammation or leucopoietic activation, assessed by [^{18}F]FDG-PET uptake in the spleen and bone marrow. Possible explanations may include the reduced statistical power of the investigated cross-sectional cohort, which included patients without established atherosclerosis and with low global cardiovascular risk, as reflected by an average Framingham Risk score below 2%. In this regard, recent studies have shown that neuroimmune interfaces assemble in human atherosclerosis and are primarily located in the adventitia,[7] thus at the very limit of technical detection of current state-of-the-art metabolic imaging techniques and possibly underappreciated at early disease stages in a cohort of subjects with subclinical atherosclerosis. Hence, while the hypothesis of higher inflammatory activation is still plausible (*Graphical Abstract*), this cannot be concluded from the current study, and investigations in prospective cohorts in humans together with mechanistic studies in animal models are warranted. The identification of neuroinflammatory networks responsible for atherosclerosis may lead to new therapeutic options.

The current article raises further awareness of the major impact of psychological stress on cardiovascular health and disease, with implications for clinical routine. The detection of subclinical atherosclerosis in young patients (median age 37 years) despite a low risk of cardiovascular events based on traditional risk factors raises the question of the proper cardiovascular preventive strategies. The association between cardiovascular events and PTSD is strong and consistent in multiple cohorts (*Graphical Abstract*).[15] The current study shows that structural impairments in the cortico-limbic circuits can be detected by magnetic resonance imaging and are associated with atherosclerosis development. Whether these findings could translate into novel diagnostic strategies for the cardiovascular risk stratification of these patients or prognostic markers of therapeutic response will require multicentre prospective clinical trials. Similarly, further studies should establish whether these

patients, as well as patients with other forms of chronic psychological stress, would benefit from cardiovascular preventive strategies.

In conclusion, the study by Gharios *et al.* provides important insights into the potential relevance of the cortico-limbic inflammatory networks in human atherosclerosis and its association with chronic psychological stress. While future research is required to delineate the complexity of the neural connections between the brain and the cardiovascular system, future studies may hold the promise of the development of novel therapeutic interventions in cardiovascular–brain circuits to treat atherosclerosis beyond current lipid-lowering and anti-inflammatory therapies.

Declarations

Disclosure of Interest

The authors declare no disclosure of interest for this contribution.

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References

1. Nabi H, Kivimäki M, Batty GD, Shipley MJ, Britton A, Brunner EJ, *et al.* Increased risk of coronary heart disease among individuals reporting adverse impact of stress on their health: the Whitehall II prospective cohort study. *Eur Heart J* 2013;**34**:2697–705. https://doi.org/10.1093/eurheartj/eht216
2. Rosengren A, Hawken S, Ôunpuu S, Sliwa K, Zubaid M, Almahmeed WA, *et al.* Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case–control study. *Lancet* 2004;**364**:953–62. https://doi.org/10.1016/S0140-6736(04)17019-0
3. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, *et al.* European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–701. https://doi.org/10.1093/eurheartj/ehs092
4. Hinterdobler J, Schott S, Jin H, Meesmann A, Steinsiek AL, Zimmermann AS, *et al.* Acute mental stress drives vascular inflammation and promotes plaque destabilization in mouse atherosclerosis. *Eur Heart J* 2021;**42**:4077–88. https://doi.org/10.1093/eurheartj/ehab371
5. Tawakol A, Ishai A, Takx RAP, Figueroa AL, Ali A, Kaiser Y, *et al.* Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. *Lancet* 2017;**389**:834–45. https://doi.org/10.1016/S0140-6736(16)31714-7
6. Poller WC, Downey J, Mooslechner AA, Khan N, Li L, Chan CT, *et al.* Brain motor and fear circuits regulate leukocytes during acute stress. *Nature* 2022;**607**:578–84. https://doi.org/10.1038/s41586-022-04890-z
7. Mohanta SK, Yin C, Weber C, Godinho-Silva C, Veiga-Fernandes H, Xu QJ, *et al.* Cardiovascular brain circuits. *Circ Res* 2023;**132**:1546–65. https://doi.org/10.1161/CIRCRESAHA.123.322791
8. Mohanta SK, Peng L, Li Y, Lu S, Sun T, Carnevale L, *et al.* Neuroimmune cardiovascular interfaces control atherosclerosis. *Nature* 2022;**605**:152–9. https://doi.org/10.1038/s41586-022-04673-6
9. Yin C, Ackermann S, Ma Z, Mohanta SK, Zhang C, Li Y, *et al.* Apoe attenuates unresolvable inflammation by complex formation with activated C1q. *Nat Med* 2019;**25**:496–506. https://doi.org/10.1038/s41591-018-0336-8
10. Wang Z, Zhang X, Lu S, Zhang C, Ma Z, Su R, *et al.* Pairing of single-cell RNA analysis and T cell antigen receptor profiling indicates breakdown of T cell tolerance checkpoints in atherosclerosis. *Nat Cardiovasc Res* 2023;**2**:290–306. https://doi.org/10.1038/s44161-023-00218-w
11. Hsueh B, Chen R, Jo Y, Tang D, Raffiee M, Kim YS, *et al.* Cardiogenic control of affective behavioural state. *Nature* 2023;**615**:292–9. https://doi.org/10.1038/s41586-023-05748-8
12. Siedlinski M, Carnevale L, Xu X, Carnevale D, Evangelou E, Caulfield MJ, *et al.* Genetic analyses identify brain structures related to cognitive impairment associated with elevated blood pressure. *Eur Heart J* 2023;**44**:2114–25. https://doi.org/10.1093/eurheartj/ehad101
13. Gharios C, van Leent MMT, Chang HL, Abohashem S, O'Connor D, Osborne MT, *et al.* Impaired cortico-limbic interactions associate with atherosclerosis across a spectrum of stress exposure. *Eur Heart J* 2024;**45**:1753–64. https://doi.org/10.1093/eurheartj/ehae149
14. Vaccarino V, Goldberg J, Rooks C, Shah AJ, Veledar E, Faber TL, *et al.* Post-traumatic stress disorder and incidence of coronary heart disease: a twin study. *J Am Coll Cardiol* 2013;**62**:970–8. https://doi.org/10.1016/j.jacc.2013.04.085
15. Akosile W, Colquhoun D, Young R, Lawford B, Voisey J. The association between post-traumatic stress disorder and coronary artery disease: a meta-analysis. *Australas Psychiatry* 2018;**26**:524–30. https://doi.org/10.1177/1039856218789779