Unveiling the heart’s silent whisperer: study of stress and the brain–heart connection in Europe

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This editorial refers to ‘Imaging of the brain–heart axis: prognostic value in a European setting’, by N. Mikail et al., https://doi.org/10.1093/eurheartj/ehae162.

Graphical Abstract

Dysregulation of the prefrontal cortex and amygdala relationship by chronic stress has direct effects on the cardiovascular system, via the hypothalamic-pituitary-adrenal (HPA) axis. These effects, which include include vasoconstriction, increased vascular resistance, increased heart rate, and decreased heart rate variability (HRV), are potentiated by SNS hyperactivation, which promotes the release of norepinephrine into the systemic circulation. Activation of the HPA axis results in the release of cortisol from the adrenal cortex, which promotes cardiometabolic disease in the form of hypertension, increased adiposity, and insulin resistance. Subsequent vascular remodelling can lead to hypoperfusion, and potentially further dysregulation of the relationship between the prefrontal cortex and amygdala.
The intersection of psychological stress and cardiovascular health has long intrigued the medical community, spurring numerous studies to understand how our mental state influences heart disease. The work performed by Mikail et al. and published in the current issue of the European Heart Journal further this quest, leveraging advanced imaging technologies to explore the prognostic significance of stress-related neural activity (SNA) on cardiovascular outcomes, as previously demonstrated. This Editorial seeks to delve deeper into the study’s implications, methodologies, and findings, and to consider its place within the broader landscape of cardiovascular research. The concept of a brain–heart axis is not new but has lacked concrete evidence until recent advancements in imaging technologies. A burgeoning field has included findings linking brain structure and function with heart structure, elucidating the mechanisms behind mental stress-induced myocardial ischaemia, and associated SNA with Takotsubo syndrome. As well as work looking at how brain function may influence cardiovascular health, previous studies have demonstrated a relationship between vascular risk and cognitive function, suggesting that vascular remodelling may cause cerebral hyperperfusion, and ultimately poorer cognitive function. In sum, these findings suggest a bidirectional relationship, which could result in a negative feedback loop of diminishing brain and heart health. If proven correct, complementary clinical care would be vital in alleviating these health burdens. Following in that vein, the study by Mikail et al. presents a unique approach by using 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) to explore the prognostic value of SNA for cardiovascular outcomes. Unlike previous studies of cardiovascular outcomes which have focused more on the direct cardiac effects of stress, as well as physical risk factors and their management, this research extends the understanding by linking brain activity directly to heart health. It diverges from prior literature by showing that while SNA is a significant predictor of all-cause mortality, its predictive value for major adverse cardiovascular events (MACE) is less definitive, emphasizing the complexity of the brain–heart connection and suggesting a nuanced influence of psychological stress on cardiovascular health compared with earlier findings.

Focusing on a cohort of 963 patients, the study meticulously relates FDG-PET/CT findings with MACE and all-cause mortality over an extended follow-up period, accounting for the effects of basic demographics, cardiovascular risk factors, comorbidities, sociocultural variables, medication, laboratories, and echocardiographic imaging. This large-scale analysis, set in a clinically diverse European population, adds a critical dimension to our understanding of SNA and cardiovascular risk, adding to previous studies in American and Asian cohorts.

The revelation that SNA serves as a robust predictor of all-cause mortality, yet offers unclear prognostic value for MACE after accounting for several groups of confounders, ignites a fascinating debate on the mechanisms at play. Investigation of the lateralization of brain stress responses was also conducted, which showed that the strongest SNA–MACE and SNA–all-cause mortality associations were derived from the left amygdala. Complex, lateralized responses to fear and pain are well documented for the amygdala, and highly depend on the driving stimuli. These findings suggest a complex interplay between SNA and cardiovascular pathology, hinting at the possibility that SNA could be a marker of systemic vulnerability rather than a direct cause of specific cardiovascular events. Indeed, Hu et al. highlight the myriad ways in which neural activity can influence cardiovascular health via sympathetic and parasympathetic pathways, stimulating the production of many cytokines and hormones, with distinct purported causal pathways between the heart and brain for hypertension, congestive heart failure, and metabolic syndrome. More research is needed investigating the demonstrated links between macroscopic clinical imaging of heart and brain, and the mediating immune and hormonal systems, for example work by Ghanios et al., which may broaden the clinical factors to consider for MACE. The bidirectional nature of the relationship complicates investigation further still.

The minimal inclusion criteria and retrospective nature of the study are real strengths in posing a real-world assessment of SNA with the benefit of hindsight, but can also confound inference with a lack of data around the emotional well-being of patients, which can have significant effects on amygdala activity. Additionally, as discussed in the paper, the relationship between SNA and MACE can be complicated somewhat by age, as the trajectory of cortical–subcortical activity into late life is still an intense area of study, which is relevant given younger patients in this study profited more from incorporating SNA into their MACE risk profile. It is also important to note that there were more than twice as many patients suffering all-cause mortality as there were with MACE, which contributes partly to the difference in statistical significance between SNA and MACE, and SNA and all-cause mortality. Nonetheless both subgroups of patients represent sizeable cohorts.

The application of FDG-PET/CT imaging in this study is both a methodological triumph and a challenge. While it enables unprecedented insight into the metabolic activity of stress-related brain regions and their impact on heart health, it also raises questions about the accessibility and practicality of such advanced diagnostics in routine clinical practice. While this imaging methodology is considered standard of care in this Swiss institution, this may not be the case in many medical institutions internationally. This is particularly important as institutions in regions with a higher socio-economic status (SES) are more likely to have the resources to conduct multimodal multiorgan imaging as routine care, whereas individuals in lower SES regions are more likely to have higher stress burdens, representing a larger potential benefit of using SNA as a prognostic tool. The authors highlight the study’s European cohort composition, yet they fail to provide a description of the ethnic background of the study population, which further hinders assessing the translatability of the findings.

From a clinical perspective, the study calls for a paradigm shift towards a more holistic view of cardiovascular risk assessment, incorporating mental health and stress management as integral components of heart disease prevention and treatment. However, the practical application of SNA imaging in everyday clinical settings remains a significant hurdle, necessitating further research to refine and democratize this technology. This research can be expanded through the incorporation of additional evaluations employing both magnetic resonance brain and cardiovascular imaging alongside PET. Such an approach would enable the association of FDG-PET results with a detailed brain circuitry map and elucidate the connections within the blood vessels and heart.

The study paves the way for a plethora of research opportunities, inviting a closer examination of the specific brain regions involved in the stress response and their direct or indirect influence on cardiovascular health. Furthermore, it underscores the need for targeted interventions that could mitigate the impact of psychological stress on the heart, potentially offering new therapeutic avenues for at-risk populations.

In summary, the study by Mikail et al. represents a seminal contribution to the evolving narrative of cardiovascular research. By bridging the gap between neurology and cardiology, it offers fresh perspectives on the prevention, diagnosis, and management of heart disease, grounded in a comprehensive understanding of the brain–heart axis. As we move forward, the study’s findings challenge us to think beyond the heart itself and consider the broader psychological and neural context in which cardiovascular disease develops and progresses.
Declarations

Disclosure of Interest
All authors declare no disclosure of interest for this contribution.

References