# The brain connection between stress and heart: a convincing research opportunity to reduce risk and gender disparity in cardiovascular disease

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The influence of stress on cardiovascular disease is an accepted fact.[1–3] Several studies have demonstrated that the various forms of psychosocial distress can adversely influence patients with cardiovascular disease.[4–7] More difficult is to identify the involved mechanisms and even more difficult is to translate this knowledge in treatments or in behavioral changes aimed at reducing or eliminating these adverse effects.[2]

Starting from the studies on the complex pathways involved in the reception of stress by our brain, various groups have addressed the amygdala as important node of the salience network, implicated in the transfer of stressful stimulations on the cardiovascular system by means of sympathetic or neuroendocrine connections, such as the hypothalamic-pituitary-adrenal axis.[8–13] In particular, higher levels of stress have been shown to produce an increase in amygdalar activity detected by [$^{18}$F]-Fluorodeoxyglucose ([$^{18}$F]FDG) Positron Emission Tomography (PET) imaging.[13–16] In turn, this augmented activity seems related to various adverse mechanisms, which have unfavorable prognostic effects, such as proinflammatory changes, the occurrence of diabetes, and visceral adiposity.[13–15]

On the other hand, gender differences have emerged both with regard to the relationship between stress and cardiovascular disease and to the presence of brain changes involved in the cardiovascular response to stress.[17–21] This requires that the baseline status to be used as reference for stress-induced changes in the involved areas must be established taking into account both age and sex.

In the present issue of the JNC, Haider et al have examined a cohort of patients submitted to [$^{18}$F]FDG PET for oncologic indications, after having excluded the presence of clinical cardiovascular disease.[22] The Authors have measured the amygdalar activity to establish the range of normal values and whether age or sex have any influence on them. They have demonstrated that amygdalar activity in men decreases with age, while in women, no age-related changes have been observed.[22]

The Authors belong to a group that has already intensively addressed the issue of the potential implications of amygdalar activity as a marker of prognosis in patients with cardiovascular disease.[16,21] Thus, there can be no doubts about the robustness of the provided results and about their reliability. The main problem is that of their usefulness. The Authors conclude that the sex-dependent changes in amygdalar activity must be taken into account when using this metrics as a risk stratification tool for patients with suspected cardiovascular disease.[22] But is it a reasonable clinical scenario? Probably not, because there are currently several grounds that make this hardly feasible. First of all, in patients with ischemic heart disease, the execution of [$^{18}$F]FDG PET for amygdalar activity assessment is completely out of the standard of care, since [$^{18}$F]FDG PET is rarely if ever performed for cardiac indications, with the sole of exceptions of few viability studies, valvular or device infection detection or assessment of possible cardiac involvement in sarcoidosis, all circumstances in which the additional value of amygdalar activity measurement would be almost negligible. Given the pressure on PET facilities for performing

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oncological studies, it is very unlikely to foresee an additional use of dedicated [$^{18}$F]FDG PET examinations for prognostic purposes, even if it is limited to brain imaging, since the available slots for cardiac PET are already badly needed for myocardial perfusion studies.[23] So far, the studied cohorts have mainly been selected among oncologic patients. The routine additional assessment of amygdalar activity in these subjects, under the assumption that many of them are as well affected by cardiovascular disease, could be considered, but technical and logistic issues, together with the lacking demonstration of true clinical advantages, make this option unrealistic.

So, what could be the usefulness of the present study? Indeed, what is apparent, looking at the literature on the relationship between brain and cardiovascular disease, it is the difficulty to establish the criteria to assess the efficacy of all possible improvements of psychosocial conditions that should prevent the unfavorable effects of stress.[1–3] Epidemiological studies aimed at this are by definition difficult to plan, expensive, and require prolonged follow-up on large populations.[2] In this regard, the availability of reliable surrogate endpoints to establish the baseline degree of psychosocial distress and subsequently the possible treatment-related improvements would be of the utmost value. Although the role of amygdalar activation is by no means definitely clarified, the converging evidence that put this structure in the middle of the stress-related network that connects brain to the cardiovascular system could support the use of amygdalar activity measurement.[8–16] For this aim, the study by Haider et al helps defining the normality range on which the presence and the regression of pathologic changes must be assessed.[22]

As an additional remark, the different behavior of amygdalar activity according to sex reinforces the notion that women present with a quite different pattern of cardiovascular disease than men, with higher prevalence of non-obstructive causes of ischemia and of stress-related stimulations.[19,20] The large amount of data that confirms this, from the higher incidence of stress (Takotsubo) cardiomyopathy in women to the higher rate of ischemic responses to mental stress in female patients, to the recent demonstration of a significant increase in events according to higher psychosocial distress in women but not in men, encourages to focus with particular attention to this side of cardiovascular disease in women.[7,24–28] Hopefully, the further clarification of this higher susceptibility to psychosocial stress could be helpful to improve the treatment of ischemic heart disease in women. Several data suggest that women are as well more sensible to the biological changes that stress induces, and not just to the stress-induced worsening of potentially harmful behaviors.[17] In this regard, markers of stress-related changes such as amygdalar activity could be extremely important. Particularly, for this critical aim of improving women health, further studies on the stress-related relationships between brain and cardiovascular system, facilitated by the reference data offered by the present study, are highly desirable.

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