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EDITORIAL

Brain–heart connection in Takotsubo syndrome before onset

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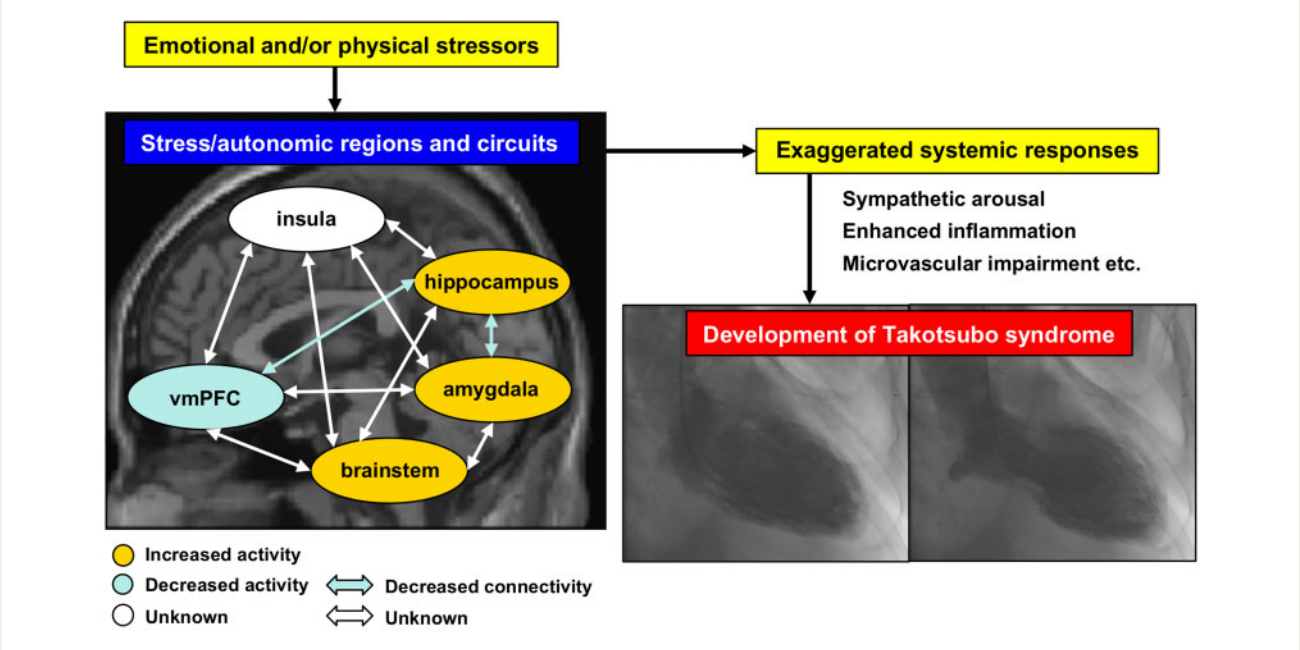
This editorial refers to 'Stress-associated neurobiological activity associates with the risk for and timing of subsequent takotsubo syndrome', by A. Radfar *et al.*, doi:10.1093/eurheartj/ehab029.

A brain–heart connection has been long proposed as a critical factor for development of Takotsubo syndrome (TTS), also known as 'stress-induced cardiomyopathy'.[1] As physical and mental stress preceded the majority of cases in TTS,[2] stress-associated brain



Graphical abstract Possible involvement of brain–heart connection for the onset of Takotsubo syndrome. Under abnormal activity and connectivity of the stress/autonomic brain regions, emotional and/or physical stressors may induce exaggerated systemic responses, leading to development of Takotsubo syndrome. The picture of the brain is from the magnetic resonance imaging template available in the free software SPM12. The left ventriculogram of a patient with Takotsubo syndrome is from Suzuki *et al.*[7] vmPFC, ventromedial prefrontal cortex.

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regions, such as the limbic system (the insula, the hippocampus, the amygdala, etc.), the ventromedial prefrontal cortex (vmPFC), and the brainstem have been hypothesized as neural substrates in TTS pathogenesis.[3–10] This notion is also consistent with the catecholamine hypothesis for TTS[1] because sympathetic activity is augmented by increased activity of the stress-associated regions, which largely overlap with brain autonomic centres.[3] In a review of 569 consecutive patients who were admitted within 24 h after the onset of an acute ischaemic stroke, including seven TTS patients, insular damage was demonstrated as a predominant feature in TTS.[4] Lesions of the brainstem, which has autonomic centres, such as the solitary nucleus and rostral ventromedial medulla, relate to TTS onset in relapses of multiple sclerosis.[5,6] These neurological cases support the notion that damage of the limbic system and the brainstem is associated with development of TTS.

Brain single-photon emission computed tomography shows that brain activity, including the hippocampus and the brainstem, is increased at 1–4 days after TTS onset.[7] This abnormal brain activation is relieved but remains to some extent even after full recovery of cardiac wall motion abnormalities (28–39 days after onset).[7] In contrast, activity of the vmPFC is reduced through both acute and chronic phases of TTS.[7] Analysis of brain structural and functional magnetic resonance images demonstrate that atrophy of the insula and the amygdala and their altered connectivity with other brain regions, including the vmPFC and the hippocampus, are found in TTS patients as compared with controls even at 1 year after onset.[8,9] These neuroimaging findings after TTS onset suggest a long-lasting psychological stress in TTS as well as the association of abnormal neural activity with development of TTS.[8,9]

The study by Radfar *et al.*, published in this issue of the *European Heart Journal*,[10] is the first to assess cerebral [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) prior to the onset of TTS. The amygdala activity (AmygA) was measured retrospectively and manually in 104 patients (median age 67.5 years, 72% female, 86% with malignancy) who underwent clinical ^{18}F-FDG-PET/CT imaging, including 41 who subsequently developed TTS (median 2.2 years after imaging) and 63 matched controls. Patients with subsequent TTS had higher baseline AmygA after adjusting for TTS risk factors (P = 0.038). Higher AmygA was associated with greater odds for developing TTS in adjusted regression analyses [standardized odds ratio (OR) 1.64, 95% confidence interval (CI) 1.03–2.61, P = 0.036] and independently predicted subsequent onset of TTS after adjustment for TTS risk factors [standardized hazard ratio (HR) 1.643, 95% CI 1.189–2.270, P = 0.003]. Among the patients who developed TTS, those with higher AmygA (>mean 1 SD) developed TTS ∼2 years earlier compared with those with lower AmygA (β –2.72, 95% CI –5.12 to –0.32, P = 0.028). These relationships between AmygA and TTS were even robust after adjusting for activity of the vmPFC, which has an important role in reducing stress responses.[3] Although having intrinsic limitations of retrospective and manual (not automated, not whole-brain) analysis, these findings by Radfar *et al.* shed light on the brain–heart connection representing a neurobiological mechanism of TTS development[3–10] (*Graphical abstract*).

The work by Radfar *et al.* raises the possibily of at least two future directions. First, it still remains unclear whether AmygA and/or activity of other stress/autonomic-associated brain regions are also associated with relapse of TTS. The rate of recurrence of TTS is 1.8% per patient-year, with a span of 25 days to 9.2 years after the first event.[2] One interesting study reports that mental stress evokes regional cardiac wall motion changes (perfusion defects and/or wall motion abnormality) in 16 out of 22 TTS patients at 1 month after onset, while none of 11 controls has stress-induced abnormalities.[11] Three patients who have abnormal cardiac response to mental stress experienced TTS recurrence at an interval of 6 ± 4 months.[11] It would be worth examining whether patients with abnormal activity of stress/autonomic-associated brain regions have a higher recurrence rate of TTS. Second, no therapeutic option is currently available for the abnormal brain activity in TTS patients. Improvement in symptoms of post-traumatic stress disorder by cognitive behavioural therapy is associated with reduced AmygA,[12] indicating that an intervention to stress and resultant improvement in abnormal activity of stress/autonomic-associated brain regions may be effective for decreasing the risk of TTS development.

Finally, the heart–brain connection is not a specific phenomenon of TTS but is widely noted in patients with cardiovascular diseases. Increased AmygA may also predict the risk of other stress-related cardiovascular and metabolic diseases.[13] The activity of the hippocampus, which is lower in patients with chronic heart failure, is associated with depression and cognitive impairment.[14] Chronic heart failure patients with higher hippocampal activity may also experience more advanced cardiac remodelling as compared with those with lower hippocampal activity.[15] Heightened stress-associated neural activity may represent a therapeutic target to reduce TTS as well as other stress-related cardiovascular diseases, including chronic heart failure.

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