# Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study

*Ahmed Tawakol*, Amorina Ishai*, Richard AP Takx, Amparo L Figueroa, Abdelrahman Ali, Yannick Kaiser, Quynh A Truong, Chloe JE Solomon, Claudia Calcagno, Venkatesh Mani, Cheuk Y Tang, Willem JM Mulder, James W Murrough, Udo Hoffmann, Matthias Nahrendorf, Lisa M Shin, Zahi A Fayad†, Roger K Pitman†*

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*These authors contributed equally

†These authors contributed equally

**Cardiology Division** (A Tawakol MD), **Cardiac MR PET CT Program** (A Tawakol, A Ishai MD, R A P Takx MD, A L Figueroa MD, A Ali MD, Y Kaiser BS, Prof U Hoffmann MD), **and Department of Psychiatry** (Prof R K Pitman MD), **Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; Radiology Department, Weil Cornell Medical College, New York, NY, USA** (Q A Truong MD); **Translational and Molecular Imaging Institute** (C J E Solomon BS, C Calcagno MD, V Mani PhD, C Y Tang PhD, Prof W J M Mulder PhD, Prof Z A Fayad PhD), **and Department of Psychiatry** (J W Murrough MD), **Icahn School of Medicine at Mount Sinai, New York, NY, USA; Center for Systems Biology, Massachusetts General Hospital, Boston, MA, USA** (M Nahrendorf MD); **and Department of Psychology, Tufts University, Medford, MA, USA** (L M Shin PhD)

Correspondence to: Dr Ahmed Tawakol, Integrative Bio-Imaging Program and Cardiac MR PET CT Program, Massachusetts General Hospital and Harvard Medical School, 165 Cambridge Street, Boston, MA 02114-2750, USA **atawakol@mgh.harvard.edu**

## Summary

**Background** **Emotional stress is associated with increased risk of cardiovascular disease. We imaged the amygdala, a brain region involved in stress, to determine whether its resting metabolic activity predicts risk of subsequent cardiovascular events.**

**Methods** **Individuals aged 30 years or older without known cardiovascular disease or active cancer disorders, who underwent $^{18}$F-fluorodexoyglucose PET/CT at Massachusetts General Hospital (Boston, MA, USA) between Jan 1, 2005, and Dec 31, 2008, were studied longitudinally. Amygdalar activity, bone-marrow activity, and arterial inflammation were assessed with validated methods. In a separate cross-sectional study we analysed the relation between perceived stress, amygdalar activity, arterial inflammation, and C-reactive protein. Image analyses and cardiovascular disease event adjudication were done by mutually blinded researchers. Relations between amygdalar activity and cardiovascular disease events were assessed with Cox models, log-rank tests, and mediation (path) analyses.**

**Findings** **293 patients (median age 55 years [IQR 45·0–65·5]) were included in the longitudinal study, 22 of whom had a cardiovascular disease event during median follow-up of 3·7 years (IQR 2·7–4·8). Amygdalar activity was associated with increased bone-marrow activity ($r$=0·47; p<0·0001), arterial inflammation ($r$=0·49; p<0·0001), and risk of cardiovascular disease events (standardised hazard ratio 1·59, 95% CI 1·27–1·98; p<0·0001), a finding that remained significant after multivariate adjustments. The association between amygdalar activity and cardiovascular disease events seemed to be mediated by increased bone-marrow activity and arterial inflammation in series. In the separate cross-sectional study of patients who underwent psychometric analysis (n=13), amygdalar activity was significantly associated with arterial inflammation ($r$=0·70; p=0·0083). Perceived stress was associated with amygdalar activity ($r$=0·56; p=0·0485), arterial inflammation ($r$=0·59; p=0·0345), and C-reactive protein ($r$=0·83; p=0·0210).**

**Interpretation** **In this first study to link regional brain activity to subsequent cardiovascular disease, amygdalar activity independently and robustly predicted cardiovascular disease events. Amygdalar activity is involved partly via a path that includes increased bone-marrow activity and arterial inflammation. These findings provide novel insights into the mechanism through which emotional stressors can lead to cardiovascular disease in human beings.**

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## Introduction

Psychosocial stress is both a byproduct of adversity and an important precipitant of morbidity. Chronic stress is associated with an increased risk of cardiovascular disease,[1,2] with an attributable risk that is on par with that of other major cardiovascular risk factors.[3–5] However, little is known about the mechanisms that translate stress into cardiovascular events.

Although several factors could account for the risk of cardiovascular disease attributable to stress, the brain's salience network, an ensemble of interconnected structures involved in complex functions such as cognition and emotion, is thought to have an important role. Activation of this network, which includes the amygdala as a key component,[6] leads to hormonal, autonomic, and behavioural changes typically associated with fear and stress.[7] The amygdala's efferent projections to the brainstem participate in the sympathetic responses to stress.[8] In murine models, stress increases proliferation of haemopoietic stem cells and progenitor cells in the bone marrow, accelerates innate immune cell output and cytokine production, and potentiates atherosclerosis.[9–13] However, whether a homologous pathway exists in human beings is unknown. Furthermore, although amygdalar reactivity is known to be heightened in individuals with pre-existing atherosclerosis,[14] neither human nor animal studies have yet shown whether amygdalar activation precedes and predisposes to the subsequent development of cardiovascular events.

Activation of the neural circuitry underlying the perception of fear-related stimuli can be