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Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism

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Summary

Patients with specific neurological, psychiatric or cardiovascular conditions are at enhanced risk of cardiac arrhythmia and sudden death. The neurogenic mechanisms are poorly understood. However, in many cases, stress may precipitate cardiac arrhythmia and sudden death in vulnerable patients, presumably via centrally driven autonomic nervous system responses. From a cardiological perspective, the likelihood of arrhythmia is strongly associated with abnormalities in electrical repolarization (recovery) of the heart muscle after each contraction. Inhomogeneous and asymmetric repolarization, reflected in ECG T-wave abnormalities, is associated with a greatly increased risk of arrhythmia, i.e. a proarrhythmic state. We therefore undertook a study to identify the brain mechanisms by which stress can induce cardiac arrhythmia through efferent autonomic drive. We recruited a typical group of 10 out-patients attending a cardiological clinic. We simultaneously measured brain activity, using $H_2{}^{15}O$ PET, and the proarrhythmic state of the heart, using ECG, during mental and physical stress challenges and corresponding control conditions. Proarrhythmic changes in the heart were quantified from two ECG-derived measures of repolarization inhomogeneity and were related to changes in magnitude and lateralization of regional brain activity reflected in regional cerebral blood flow. Across the patient group, we observed a robust positive relationship between right-lateralized asymmetry in midbrain activity and proarrhythmic abnormalities of cardiac repolarization (apparent in two independent ECG measures) during stress. This association between stress-induced lateralization of midbrain activity and enhanced arrhythmic vulnerability provides empirical support for a putative mechanism for stress-induced sudden death, wherein lateralization of central autonomic drive during stress results in imbalanced activity in right and left cardiac sympathetic nerves. A right–left asymmetry in sympathetic drive across the surface of the heart disrupts the electrophysiological homogeneity of ventricular repolarization, predisposing to arrhythmia. Our findings highlight a proximal brain basis for stress-induced cardiac arrhythmic vulnerability.

Keywords: arrhythmia; autonomic; functional brain imaging; heart; midbrain

Abbreviations: HF = high frequency; HRV = heart rate variability; LF = low frequency; TCRT = total cosine R to T; TWR = T-wave residua

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Introduction

Abundant evidence implicates mental and physical stress associated with everyday living in the precipitation of sudden cardiac death (Fries *et al*., 2002; Steptoe *et al*., 2002). Death is usually due to an abnormal heart rhythm, but a mechanistic link between stress and sudden cardiac death remains elusive. Neurological conditions, including epilepsy, subarachnoid haemorrhage and cerebrovascular disease, and psychiatric conditions, such as schizophrenia, are associated with enhanced risk of arrhythmia and sudden death (Oppenheimer *et al*., 1990; Oppenheimer, 1994; Hennessy *et al*., 2002; Nei *et al*., 2004). The contribution of central neurogenic factors to the generation of arrhythmia is highlighted further in studies demonstrating pathological ECG changes elicited by stimulation of specific brain regions (Oppenheimer *et al*., 1990; Oppenheimer, 1994). Patients with existing cardiovascular disease may be particularly sensitive to stress-induced neurogenic arrhythmia, reflecting the reactivity of a compromised myocardium (Lown *et al*., 1977; Lampert *et al*., 2000). A possible mechanism linking mental stress and sudden cardiac death has been proposed whereby lateralized cortical and subcortical activation during the central processing of stress tasks is channelled ipsilaterally and results in lateralized imbalance of neural input to the heart (Lane and Jennings, 1995).

Such a hypothesis requires the demonstration of a correlation between laterality of brain activation during mental stress and an alteration in the electrophysiology in the heart in a manner which is proarrhythmic. Although such a correlation has not been demonstrated, there is nevertheless a wealth of experimental work which combines to form the basis for such a chain of events. For example, workers on the heart have shown that asymmetric or inhomogeneous recovery of excitability following cardiac activation (repolarization) creates electrical instability and provides the conditions for the development of cardiac arrhythmias (Han and Moe, 1964; Kuo *et al*., 1983; Batchvarov *et al*., 2003). The neural pathways from the brain to the heart are via the right and left sympathetic and parasympathetic nerves (autonomic nerves) which are distributed asymmetrically in the ventricular myocardium (Yanowitz *et al*., 1966; Levy and Martin, 1979). Unilateral stimulation of either right or left sympathetic nerves in animal models has been shown to induce repolarization inhomogeneity and arrhythmias, and enhance the susceptibility to ventricular fibrillation (Lown *et al*., 1977; Levy and Martin, 1979; Schwartz, 1984, 2001). Workers on the brain have provided evidence of lateralized brain function with respect to autonomic response. On the basis of the fact that the sinus node, which governs heart rate, is influenced predominantly by the right sympathetic nerves (Schwartz and Stone, 1979), several studies have shown that stimulation of the right-sided brain structures, but not the left, induces an increase in heart rate (Henry and Calaresu, 1974). These studies provide evidence for ipsilateral channelling of lateralized cerebral activation to the heart, a mechanism that accounts for the similarity of ECG T-wave changes induced by unilateral stimulation of sympathetic nerves and by stimulation of ipsilateral brain regions (Rogers *et al*., 1973). There is also human neuroimaging evidence for lateralization of cerebral activity during stress-induced autonomic cardiovascular arousal (Critchley *et al*., 2000, 2001). Moreover, stress-induced asymmetry of brain activity may be more exaggerated in patients with coronary artery disease who are at risk of stress-induced arrhythmia (Soufer *et al*., 1998).

Thus considerable evidence from different disciplines supports the notion that asymmetric brain activation is an important link between mental stress and a proarrhythmic state of the heart. A major purpose of this study was to test for correlations between laterality of brain activation during stress and a well established electrophysiological substrate for cardiac arrhythmia, increased inhomogeneity of electrical repolarization in the heart. To achieve this, we performed a collaborative study between centres for neuroscience and cardiology using simultaneous brain imaging and measurement of cardiac repolarization inhomogeneity. Earlier neuroimaging investigations reported activation of limbic cortical and brainstem regions associated with sympathetic cardiovascular arousal during isometric handgrip and mental arithmetic stress challenges (Critchley *et al*., 2000, 2001). The present study replicates these experimental methods to test specifically for an association between abnormalities in the electrical repolarization of the heart and lateralization of brain activity during mental and physical stress in a cardiological patient group at risk of neurogenic, stress-induced arrhythmia.

Methods

Participants

Ten people (aged 47–72 years, mean 57 years, eight male, two female) were recruited to participate in our functional neuroimaging experiment from out-patients attending a cardiology clinic. They were recruited in an unbiased way to represent a mixed sample of typical cardiology patients. Each gave fully informed written consent to participate in a study approved by the local Ethics Committee (Joint UCL/UCLH Committees on the Ethics of Human Research). A series of detailed cardiological investigations had been conducted in every subject, including coronary angiography. Haemodynamically significant coronary artery disease, i.e. >50% stenosis of at least one major vessel, was present in four subjects (two patients had previous inferior myocardial infarction). Minor coronary artery disease was present in two subjects (one with mild dilated ventricular cardiomyopathy); one further subject had mild dilated ventricular cardiomyopathy and, in three subjects, no cardiac cause for chest pain was found. Seven patients were taking peripherally acting β-blockers (atenolol) (Table 1).

Experimental tasks and ECG

Each subject was scanned using $H_2{}^{15}O$ PET while performing two replications of mental and physical stress tasks and corresponding control conditions. In the mental stress task, the subject was required to perform (to themselves) rapid continuous serial subtractions of

Table 1 *Clinical features of patients participating in the study*

	Sex	Age	BMI	HR	Diagnosis	Coronary anatomy	LV function	Medication
1	M	53	24	56	Normal heart, mild hypertension	Normal	Normal	Atenolol
2	M	61	27	92	Normal heart	Normal	Normal	Nil
3	M	72	28	58	Minor CAD, mild dilated cardiomyopathy	Minor diffuse CAD	Mild LV systolic impairment	Ramipril, atenolol
4	F	47	24	66	CAD-post CABG	Moderate diffuse CAD, graft stenosis	Normal	Atenolol
5	F	59	31	74	Bicuspid aortic valve	Normal	Normal	Nil
6	M	58	26	62	CAD, exercise-induced VT	Diffuse disease	Normal	Atenolol
7	M	57	24	67	Minor CAD	Minor narrowing of LAD	Normal	Nil
8	M	57	24	66	CAD inferior MI hypertension	LAD moderate stenosis, Cx moderate stenosis, RCA irregular	Anteroseptal akinesis	Ramipril, atenolol
9	M	50	25	68	CAD inferior MI	Severe in-stent restenosis of RCA	Mild inferior hypokinesia	Atenolol
10	M	62	27	75	Dilated cardiomyopathy	Normal	Moderate global impairment	Atenolol

BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; Cx = circumflex coronary artery; HR = heart rate; LAD = left anterior coronary artery; LV = left ventricular; MI = myocardial infarction; RCA = right coronary artery; VT = ventricular tachycardia.

7 from a cued starting point over a 3 min period. In the corresponding low-stress 'effortless' control condition, the subject was required to count to themselves slowly from a cued starting point over 3 min. In the physical stress challenge, the subject was required to maintain an isometric handgrip squeeze against resistance at a steady pressure of 33% their maximal squeeze strength, for 3 min. In the corresponding low-stress physical control condition, the subject was required to maintain a minimal squeeze, below 10% of their maximal squeeze strength, for 3 min. Prompts for the onsets of each task were presented to the subject by a video monitor. These cognitive and physical stress conditions and their control tasks represent replications of two previous PET studies examining central autonomic control (Critchley *et al*., 2000, 2001).

ECG was recorded continuously in all subjects during scanning using two devices: a three-channel ambulatory ECG recorder (Delmar Reynolds Medical Ltd) and 12-lead digital ambulatory ECG recorder (SEER MC, GE Marquette, Milwaukee, WI). The three-channel ECG recording was used for measurement of heart rate variability (HRV) using the Pathfinder 700 system, whilst the 12-lead digital recording was used for analysis of ventricular repolarization. High- (HF, 0.15–0.4 Hz) and low-frequency (LF, 0.04–0.15 Hz) components of HRV, which reflect parasympathetic and sympathetic effects on heart rate, respectively (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), were computed from 1 and 2 min intervals from all normal to normal RR intervals (i.e. 1 min intervals were used to calculate HF influences and 2 min intervals to calculate LF influences on HRV). The heterogeneity of ventricular repolarization was analysed using a custom-developed software program (Acar *et al*., 1999; Malik *et al*., 2000) and was quantified by two parameters, namely TCRT (cosine of the angle between the spatial QRS and T vectors) and T-wave residua, TWR (i.e. proportion of the non-dipolar components of the T wave). Both parameters describe more comprehensively, and have better reproducibility, than other parameters of ventricular repolarization such as QT interval and QT dispersion (Acar *et al*., 1999; Malik *et al*., 2000). Prospective studies have demonstrated significant predictive power for cardiac and arrhythmic mortality of both TCRT and TWR (Zabel *et al*., 2000, 2002; Batchvarov *et al*., 2003).

PET scan acquisition and preprocessing

Scans of the distribution of $H_2{}^{15}O$ were obtained using a Siemens/CPS ECAT EXACT HR + PET scanner operated in high sensitivity 3D mode. Subjects received a total of 350 MBq of $H_2{}^{15}O$ over 20 s through a right antecubital cannula for each of the scans, and activity was measured during a 90 s time window while the subjects performed the task conditions. The PET images comprised i, j and k voxels ($2 \times 2 \times 3$ mm) with a 6.4 mm transaxial and 5.7 mm axial resolution (full width at half-maximum). Functional data were analysed with statistical parametric mapping (SPM2, http://www.fil.ion.ucl.ac.uk/spm/spm2.html), implemented in Matlab6.5 (Mathworks, Natick, MA). Group analyses of PET data were conducted controlling for repeated measures across subjects. Scans were first realigned with respect to each other and using a left–right symmetrical template, transformed into a standard stereotactic space (Friston *et al*., 1995*a*, *b*). In addition, scan images were also transformed by left–right spatial reflection across the midline ('flipped') to allow for form testing of bilateralism and hemispheric lateralization of responses (Friston, 2003). All images were smoothed using a Gaussian filter set at 12 mm full width at half-maximum. Regional cerebral blood flow measurements were adjusted to a global mean of 50 ml/dl/min.

Functional imaging data were analysed first to test for activity associated with effort, independent of task modality. An analytic design matrix was constructed to model each of the four tasks, controlling (as in all these analyses) for repeated measures across subjects. To identify stress-related activity shared across cognitive and physical task conditions, we used conjunction analyses (Price and Friston, 1997; Friston *et al*., 1999) to localize activity common to effortful versus effortless mental arithmetic and exercise. Separate

analyses tested for activity associated with ECG measures of repolarization inhomogeneity (TCRT and TWR), heart rate, and LF and HF power in HRV. By testing for correlations during the cognitive tasks independently from correlations during physical tasks, we could again use conjunction analyses to identify effects that were equally manifest during both mental and physical stress. In a further analysis, we modelled TCRT and TWR together to test, again using a conjunction analysis, for brain regions where activity correlated with both these regressors. By including 'standard' normalized and 'flipped' images in all the analyses, we could directly test the significance of right–left symmetry and asymmetry in regional brain activity, where symmetrical task activity is observed as a significant conjunction, and lateralized responses reflected in significant differences between unflipped and flipped (left–right mirror image) data (Friston, 2003). These analyses of lateralization effects naturally took into account all within-subject repeated measures. Since significance was tested over many brain voxels, emphasis is given to data reaching significance at a stringent threshold of $P < 0.05$, corrected for multiple comparisons across the whole brain using family wise error (similar to Bonferroni) correction. Data in Figs 2 and 3 are presented on sections of a standard template brain scan (a T1-weighted structural MRI scan derived from one subject) at $P < 0.001$, uncorrected to highlight the spatial extent of the midbrain cluster.

Results

Subjective reports, autonomic measures and indices of inhomogeneity

All 10 patients rated performance of the effortful mental arithmetic and isometric handgrip exercise tasks more demanding than the corresponding 'effortless' control conditions, consistent with induction of mental and physical stress. During effortful mental and physical stress conditions, compared with control tasks, both indices of cardiac repolarization inhomogeneity (TCRT and TWR) changed in a proarrhythmic manner (Fig. 1). Heart rate was also increased on average during mental stress compared with the control condition, but heart rate increases to effortful and effortless exercise tasks were similar in magnitude. LF (sympathetic) power in heart rate, and the ratio of LF to HF power, reflecting sympathetic/parasympathetic balance, increased on average

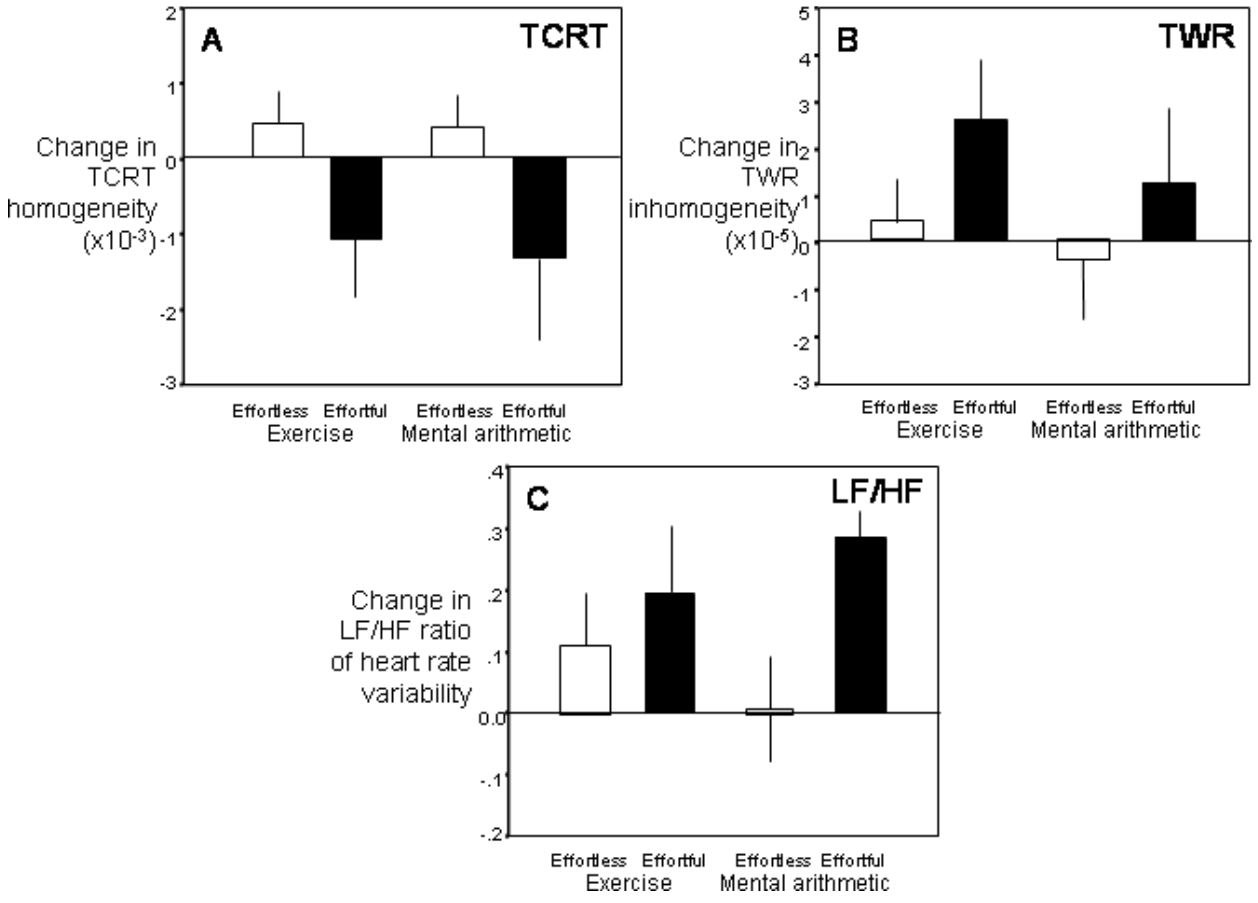

Fig. 1 Task effects on cardiac measures of arousal and inhomogeneity. Subjects performed repetitions of physical (isometric handgrip exercise) and cognitive (mental arithmetic) stress tasks, and a corresponding 'effortless' control condition, during simultaneous scanning and ECG. The plots show the mean and SE of evoked changes in (**A**) TCRT, a measure of electrical inhomogeneity in the heart, derived from the ECG T wave, (**B**) TWR, a second, independent measure of electrical inhomogeneity derived from the ECG T wave, and (**C**) the LF/HF power ratio, a measure of sympathetic to parasympathetic balance. These plots show a shift in the proarrhythmic state of the heart during both physical and mental stress, indicated by decreases in TCRT and increases in TWR, and stress-induced increases in sympathetic relative to parasympathetic drive to the heart, indicated by increases in the LF/HF ratio during effort.

Table 2 *Neuroimaging findings*

Region	Side	Coordinates of maximum	*Z* score	*P* value*
Activity related to decreasing TCRT (increased inhomogeneity)				
Midbrain	Right	12, −22, −22	4.40	0.050
Parahippocampal gyrus	Right	24, −40, 2	4.82	0.015
Middle occipital gyrus	Right	26, −84, 32	4.73	0.022
Cerebellar dentate nucleus	Right	35, −50, −34	4.66	0.030
Activity related to increasing TWR (increased inhomogeneity)				
Midbrain	Right	14, −14, −12	5.01	0.006
Left inferior parietal cortex	Left	–60, −58, 40	5.03	0.006
Activity common to both decreasing TCRT and increasing TWR				
Midbrain	Right	14, −16, −16	4.72	0.024
Activity related to task effort				
Midbrain	Bilateral	0, −20, −12	4.71	0.045
Cerebellar vermis	Bilateral	0, −66, −12	5.28	0.003
Activity related to increasing heart rate				
Cerebellar vermis	Bilateral	±2, −58, −24	4.78	0.034
Superior temporal gyrus	Left	–38, −38, 4	5.63	<0.001

**P* value of significance of peak voxel corrected for multiple comparisons across the whole brain using family wise error (akin to a Bonferroni correction).

during both cognitive and physical stress (Fig. 1). Individual variability across the group meant that these observations were trends, falling short of criterion significance in analysis of variance (ANOVA) analyses. However, increased repolarization inhomogeneity related to increased sympathetic cardiac influences, where TCRT correlated significantly with LF power (Spearman $\rho = -0.37$, $P < 0.01$) and LF/HF ratio (Spearman $\rho = -0.25$, $P = 0.01$). There were noteworthy trends in correlations between TWR and LF power (Spearman $\rho = 0.17$, $P = 0.08$) and TWR and TCRT ($\rho = -0.17$, $P = 0.10$).

Neuroimaging findings

We tested for correlations between regional brain activity and ECG-derived measures of inhomogeneous cardiac repolarization (degree of proarrhythmic state) and autonomic response. Importantly, we directly explored the hypothesis that predisposition to arrhythmia may arise from imbalanced right–left shifts in the central autonomic drive to the heart (Friston, 2003). In order that observed effects were attributable to stress-related autonomic activity (independent of task modality), we ensured that they were present independently in both exercise and mental arithmetic conditions [formally tested using conjunction analyses (Price and Friston, 1997; Friston *et al*., 1999)] thereby excluding activity that was specific only to either cognitive or physical task modality.

Neural activity related to ECG T-wave indices of repolarization inhomogeneity and abnormality

TCRT is a measure of the homogeneity of the 'global' direction of repolarization over the ventricles of the heart. Abnormalities in the physiological synchrony between cardiac depolarization and repolarization result in decreases in TCRT magnitude, i.e. they are proarrhythmic. Brain activity relating to decreases in TCRT during both mental and physical stress was observed unilaterally in a right midbrain region (Table 2, Fig. 2A). The degree of lateralization of activity within this midbrain region correlated with measured TCRT (Pearson $R = -0.385$, $P < 0.001$). We note that the relationship between midbrain activity lateralization and TCRT also suggested a non-linear component (Fig. 2B). Enhanced activity in regions including medial temporal lobe and cerebellum was also associated with proarrhythmic TCRT decreases. TCRT decreases were not significantly associated with bilateral or midline activity.

TWR provides an index of island-type localized variability and instability of cardiac repolarization. A proarrhythmic increase in electrical inhomogeneity is reflected in an increase in TWR magnitude (opposite in direction to TCRT). Brain activity associated with increased TWR in response to stress was also observed unilaterally in right midbrain, extending into adjoining thalamus and hypothalamus (Fig. 3, Table 2). The degree of lateralization of this midbrain activity was linearly correlated with TWR (Pearson $R = 0.394$, $P < 0.001$), but also suggested a non-linear component. Activity within left parietal lobe also correlated with TWR inhomogeneity, but there was no significant relationship between TWR and bilateral or midline activity.

TCRT and TWR represent mathematically independent measures of electrical inhomogeneity, and only a trend was observed in their inter-correlation. Nevertheless, both TCRT and TWR measures of cardiac inhomogeneity were associated with right-lateralized midbrain activity. Using a conjunction analysis approach [that requires both effects to exceed a critical level minimum T value (Friston *et al*., 1999)], we formally demonstrated involvement of the same

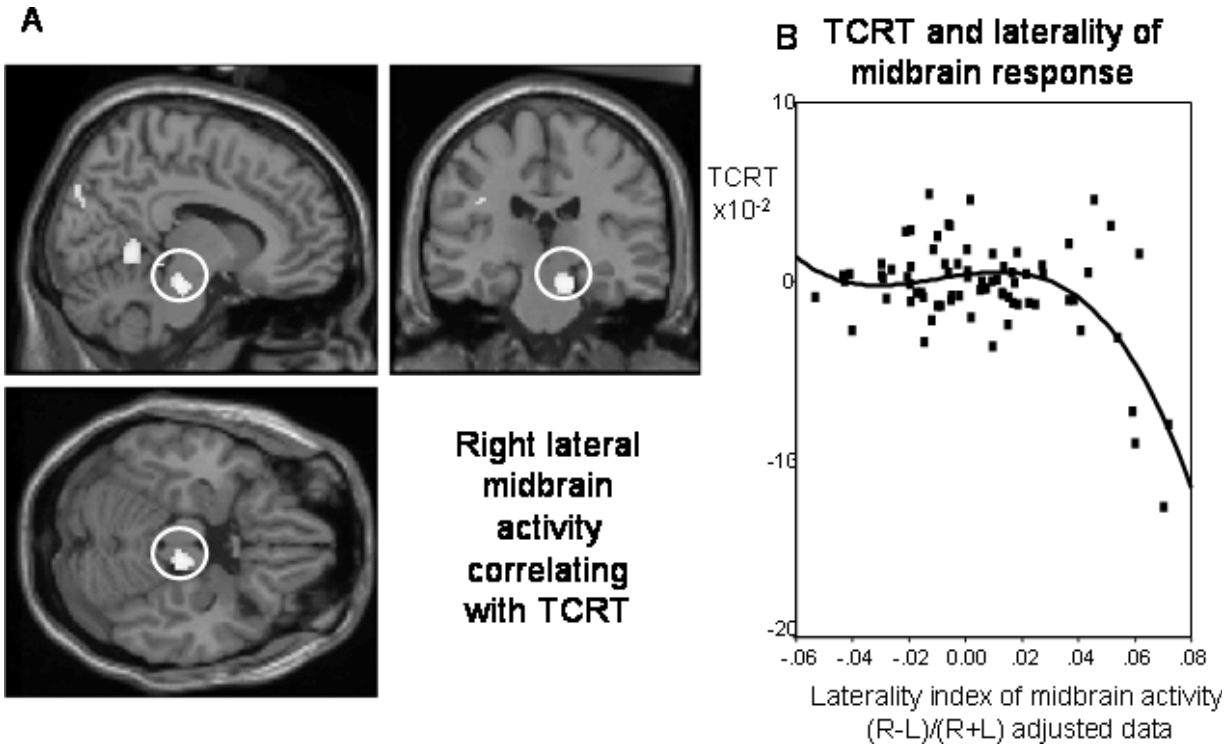

Fig. 2 Relationship of brain activity to inhomogeneity measured using TCRT. (**A**) Right-lateralized brain activity in the midbrain was associated with increases in inhomogeneity of cardiac repolarization (a proarrhythmic state), calculated from the 12-lead ECG using total cosine R to T (TCRT) (Acar *et al*., 1999; Malik *et al*., 2000), in both mental arithmetic and exercise task conditions (formally tested using a conjunction analysis). There was a significant negative linear regression between measured right-sided midbrain activity and evoked change in TCRT in both exercise and mental task challenges. Group data are plotted on sagittal, coronal and axial sections of a normalized template image at a threshold of $P < 0.001$. (**B**) Plot of evoked TCRT as a function of the laterality of midbrain activity, illustrating the correlation between a right shift in midbrain activity and a proarrhythmic effect on cardiac repolarization. The laterality index (right minus left/right plus left) was calculated from adjusted functional data at the peak of activity in the right midbrain and its contralateral homologue. A cubic regression line is fitted to the data to illustrate the non-linearity of the relationship between TCRT and asymmetric midbrain activity. This non-linear effect was driven in particular by the data from subject 8, and to a lesser extent subjects 4 and 5 (extreme lateralized activity associated with the most negative TCRT).

midbrain region in both these measures of proarrhythmic state (Table 2).

Predictive value of midbrain lateralization on arrhythmic vulnerability

We tested whether the degree of stress-induced right lateralization of midbrain response predicted proarrhythmic changes in T-wave morphology by dividing the patients into two equal groups: subjects 1, 2, 4, 5 and 8 (see Table 1) each demonstrated a peak right-sided imbalance in midbrain response (mean 5.9%). In contrast, subjects 3, 6, 7, 9 and 10 did not show significant evoked right lateralization of midbrain response (mean 0.15%) [group difference: $t(8) = 4.6$ $P < 0.002$]. In ANOVA comparisons of the two groups, we demonstrated that patients who showed significant right lateralization of midbrain activity showed significant proarrhythmic changes in both TCRT and TWR during (mental and physical) stress. In contrast, patients who did not show right imbalance of midbrain activity did not show stress-induced proarrhythmic changes in TCRT or TWR. Control tasks did not induce proarrhythmic changes in either group. These effects were confirmed as significant group $\times$ effort interactions [for TCRT, $F(3) = 3.86$, $P < 0.02$; for TWR, $F(3) = 4.15$, $P < 0.01$].

Other task-related effects

Stress (both mental and physical) was associated with midline enhancement of activity in midbrain and cerebellar vermis (where activity also correlated significantly with stress-induced heart rate increases (Table 2). In contrast to earlier studies (Critchley *et al*., 2000, 2001), we did not demonstrate co-localized activation of the same dorsal cingulate cortex region during mental or physical stress at threshold significance. At a reduced threshold (not correcting for multiple comparisons across the whole brain, but at $P < 0.001$), sympathetic-related activity increases were observed in midline cerebellum and dorsal cingulate, consistent with previous accounts of enhanced activity in these regions associated with sympathetic arousal (Critchley *et al*., 2000, 2001, 2003).

In summary, both measures of inhomogeneity of cardiac electrical repolarization were associated with asymmetric

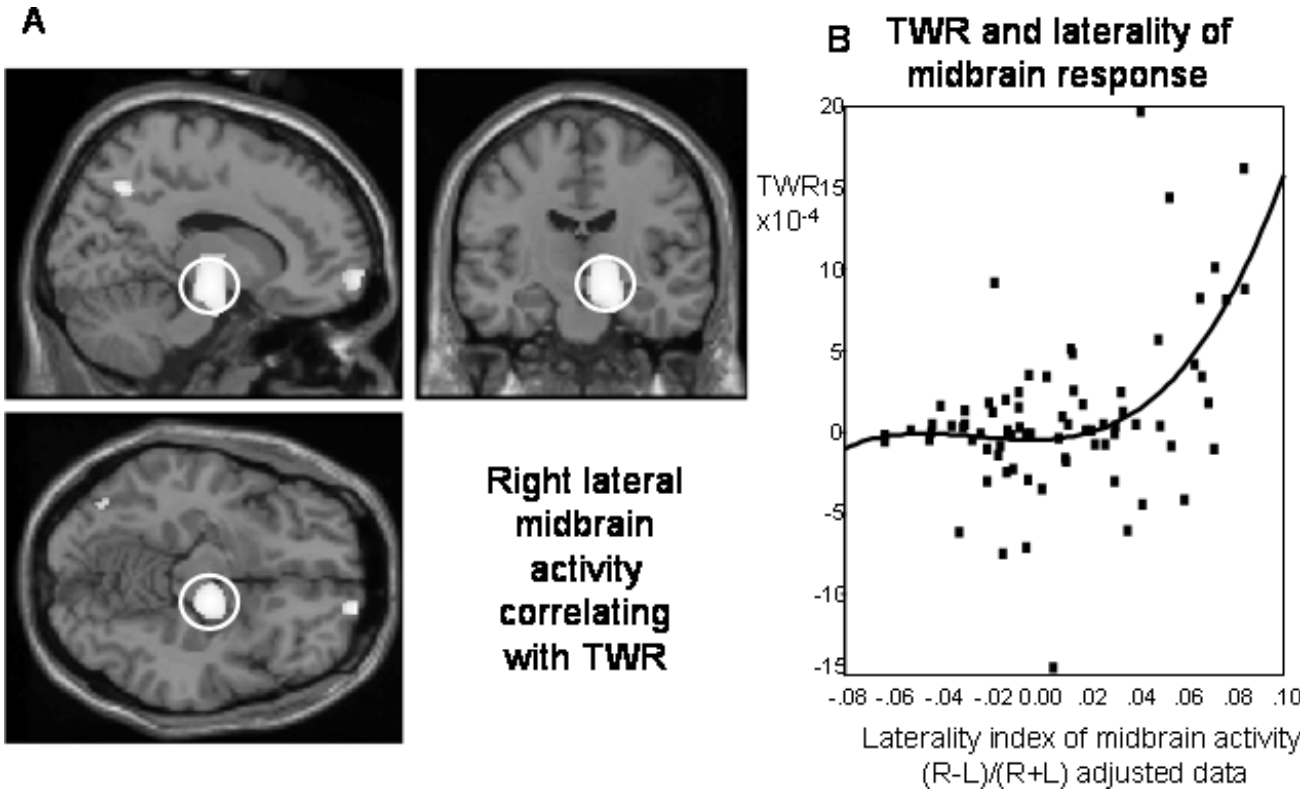

Fig. 3 Relationship of brain activity to inhomogeneity measured using TWR. (**A**) Right-lateralized brain activity in the midbrain was associated with increases in inhomogeneity of cardiac repolarization (proarrhythmic state), indexed by ECG T-wave residua (TWR) (Acar *et al*., 1999; Malik *et al*., 2000), independent of task modality. There was a significant negative linear regression between measured right-sided midbrain activity and evoked change in TCRT in both exercise and mental task challenges. Group data are plotted on sagittal, coronal and axial sections of a normalized template image at a threshold of $P < 0.001$. (**B**) Plot of evoked TWR across all scans as a function of the laterality of midbrain activity, illustrating the correlation between a right shift in midbrain activity and a proarrhythmic effect on cardiac repolarization. A cubic regression line is fitted to the data to illustrate the non-linearity of the relationship between TWR and asymmetric midbrain activity. As with TCRT, there appears to be a 'laterality' threshold at which cardiac inhomogeneity becomes apparent. This non-linear effect is driven by data from subject 2 and subject 1 (extreme lateralized activity associated with most positive TWR values).

midbrain activity. Although our imaging results represent a significant linear relationship with lateralized brain activity, closer inspection of these data suggests that there is also non-linearity in this relationship, wherein increased repolarization inhomogeneity is accentuated after right–left imbalance in midbrain activity exceeds a critical threshold. This effect was highlighted by the comparison of patients demonstrating right lateralization of midbrain response and marked proarrhythmic changes during stress with those patients showing no lateralization and no proarrhythmic changes. Inhomogeneity-related cortical and cerebellar activity may further represent the origin of modulatory influences producing a lateralization of efferent autonomic drive to the heart originating in the midbrain.

Discussion

Many neurological, psychiatric and cardiological patient groups are at risk from arrhythmia and sudden death attributable to a central neurogenic cause (Lown *et al*., 1977; Oppenheimer *et al*., 1990; Oppenheimer, 1994; Lane and Jennings, 1995; DiPasquale *et al*., 1998; Hennessey *et al*., 2002; Cheung and Hachinski, 2003; Macmillan *et al*., 2003; Nei *et al*., 2004). For example, sudden arrhythmic death in epilepsy is likely to originate from seizure activity driving efferent autonomic effects on the heart (Mameli *et al*., 1988; Oppenheimer, 1994; Nei *et al*., 2004). Emotional challenges and mental and physical stress are associated with arrhythmogenesis, again via efferent autonomic activity, and patients with pre-existing cardiac disease are especially vulnerable (Lampert *et al*., 2000). Our findings indicate a mechanism by which brain activity associated with stress and autonomic arousal may be translated into a proarrhythmic state of the heart.

Electrophysiological studies suggest that increased electrical inhomogeneity of the myocardium, during the repolarization phase of the cardiac cycle, is a major factor in the susceptibility to ventricular arrhythmias (Batchvarov *et al*., 2003). If parts of the heart recover and are ready to contract before neighbouring regions, the likelihood of an abnormal heart rhythm is greatly increased. The left- and right-sided autonomic (sympathetic) nerves are distributed asymmetrically over the ventricles, and

unilateral stimulation of either side may alter repolarization inhomogeneity (Yanowitz *et al*., 1966). Thus, repolarization inhomogeneity may reflect 'upstream' influences on the right–left symmetry of sympathetic cardiac drive, for example asymmetric brain activation in response to stress. This key question was the focus of the present study, which, for the first time, provides evidence for a mechanistic link between stress and cardiac arrhythmias at the level of the brain.

We used two measures of electrical inhomogeneity in the heart, that index abnormal distribution and time course of cardiac muscle repolarization (Acar *et al*., 1999; Malik *et al*., 2000; Zabel *et al*., 2000, 2002; Batchvarov *et al*., 2003). Increased inhomogeneity of cardiac ventricular repolarization represents the electrophysiological substrate for serious ventricular arrhythmias, facilitating ventricular tachycardia and fibrillation (Kuo *et al*., 1983). Both indices of electrical inhomogeneity in the heart, the TCRT (quantifying 'global' repolarization synchrony) and TWR (a 'local' index of inhomogeneity), were altered in a proarrhythmic manner in response to stress and were associated with abnormally lateralized midbrain activity, consistent with the proposal that imbalance of sympathetic drive to the heart represents a common basis for arrhythmic risk. Notably, the 'global' index of repolarization inhomogeneity, TCRT, was most directly related to efferent sympathetic drive, correlating with LF power and the LF/HF ratio across subjects and tasks.

Mental and physical stress is widely recognized as playing an important role in ventricular arrhythmias and sudden cardiac death. One group of subjects particularly at risk are patients with coronary artery disease. Much research has focused on describing local cardiac causes for arrhythmia, such as ischaemia. In fact, mental and physical stress can cause ischaemia, and ischaemia may precipitate ventricular tachycardia and ventricular fibrillation (Janse and Wit, 1989). Nevertheless, in a substantial number of cardiological patients, arrhythmia and death are thought to occur in the absence of ischaemia (Lampert *et al*., 2000). The potential for mental stress to predispose to arrhythmia in the absence of ischaemia is highlighted by the observation that it is easier to induce arrhythmia in at-risk patients with an implantable cardioverter defibrillator when the subjects performed an effortful mental arithmetic task (Poole and Bardy, 2000). A brain mechanism underlying the generation of arrhythmia is suggested by the clinical association of arrhythmia with neurological conditions such as epilepsy (Oppenheimer, 1994; Nei *et al*., 2004), focal brain lesions (Cheung and Hachinski, 2003) and subarachnoid haemorrhage (DiPasquale *et al*., 1998; Macmillan *et al*., 2003), and the experimental induction of arrhythmia by focal brain stimulation (Lown *et al*., 1977; Mameli *et al*., 1988). Existing evidence suggests that proarrhythmic states of inhomogeneous electrical repolarization observed in our patients during stress may result from asymmetrical sympathetic drive to the heart. In identifying neural correlates of cardiac inhomogeneity, we have localized a putative substrate underlying asymmetric autonomic influences on the heart. Anatomically, there is evidence for subcortical lateralization of efferent sympathetic pathways, with segregation of left and right responses maintained at the level of brainstem and spinal cord (Mangina and Beuzeron-Mangina, 1996). Our results suggest that a critical transitional locus exists in the midbrain region. When midbrain activation in response to stress was bilaterally symmetrical, the repolarization inhomogeneity in the heart was unchanged. However, when stress-induced midbrain activation was lateralized to the right, repolarization inhomogeneity (i.e. the arrhythmogenic substrate) was enhanced (see Fig. 4). It is noteworthy that within our limited sample of cardiology patients, the magnitude of proarrhythmic changes did not appear to be predicted by the severity of coronary artery disease, whereas these effects are apparent in some patients with normal coronary arteries.

At the level of the cerebral cortex, evidence from clinical studies and PET neuroimaging experiments suggests a right-sided dominance of cortical regions, particularly right insular and anterior cingulate cortices, in the generation of sympathetic responses (Oppenheimer *et al*., 1990; Oppenheimer, 1994; Critchley *et al*., 2000, 2001). There may be, therefore, a right hemispheric predominance of cortical influences on subcortical autonomic centres during mental and physical stress and this tendency may be expressed as a relative predominance of right sympathetic responses. Our evidence, as illustrated in Figs 2 and 3, suggests that a threshold may exist at which central sympathetic drive reaches a critical right–left imbalance at the level of the midbrain. Beyond this threshold, the electrophysiological integrity of myocardial responses is compromised, creating conditions favourable to arrhythmia. The spatial resolution of our PET study is insufficient to pinpoint the precise nuclei involved. However, both ascending influences on cortex and descending influences on autonomic activity originate within this region of midbrain and adjacent hypothalamus and thalamus. For example, electrical stimulation of the cuneiform reticular nucleus, located centrally within this activity cluster, may modulate stress-related sympathetic cardiac responses in animal experiments (Korte *et al*., 1992; Lam and Verberne, 1997). However, the adjacent parabrachial nucleus (also encapsulated within this lateralized activity cluster) projects directly to efferent autonomic tracts (in contrast to the cuneiform nucleus; Korte *et al*., 1992) and when stimulated with glutamate is associated with robust modulation of cardiovascular responses (Chamberlin and Saper, 1992). Animal studies also report activation of lateral parabrachial nucleus in response to physiological stresses (Baffi and Palkovits, 2000), suggesting the parabrachial nucleus as a plausible origin for the stress-induced cardiac effects observed in this study.

The explanation for the asymmetrical midbrain response is not clear from this study alone. Despite robust effects observed in our sample of typical cardiology patients, our findings require further exploration in extended, and perhaps more uniform, populations of both neurological and cardiological patients. One possibility is that the right-lateralized shift in midbrain activity reflects dysfunction, during stress, of a system that translates cortical activity into bilateral

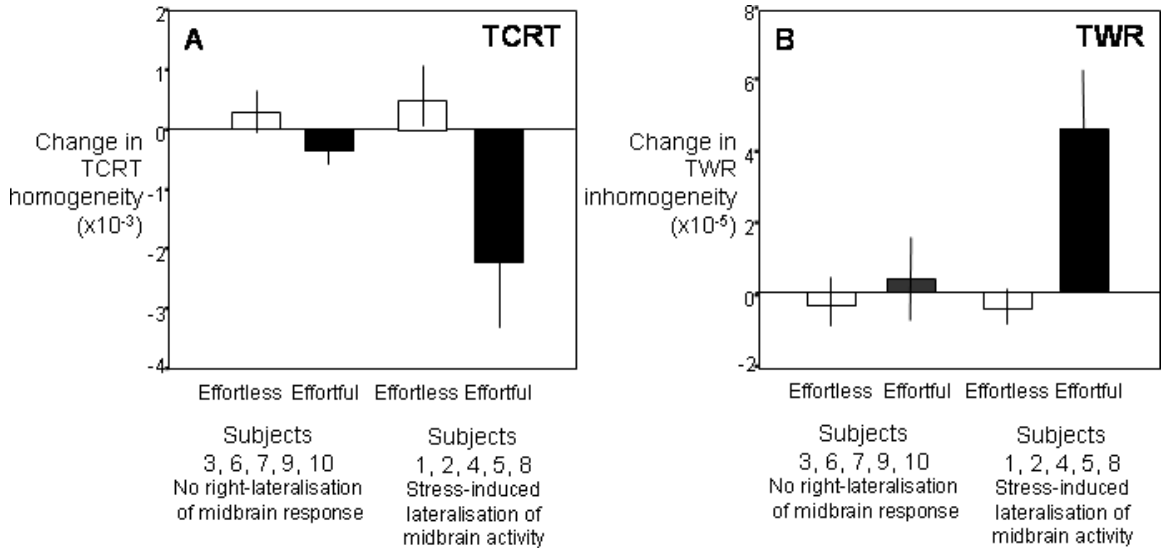

Fig. 4 Stress-induced proarrhythmic changes in heart repolarization in patients showing right lateralization of midbrain activity and those showing no right lateralization. The figures highlight the predictive significance of stress-induced lateralization of midbrain activity on arrhythmic risk. We categorized the patients into two groups according to the degree of right midbrain lateralization. (**A**) In patients showing stress-induced midbrain lateralization, effortful mental and physical stress tasks evoked proarrhythmic changes in TCRT, reflecting global increases in repolarization inhomogeneity and indexed by an increasingly negative TCRT value. In contrast, no significant changes in TCRT were observed in patients that did not demonstrate stress-induced right lateralization of midbrain response. A significant group × effort interaction was confirmed. Effortful mental and physical task effects are denoted by the filled bars and effortless control tasks by open bars. (**B**) In the same patients that demonstrated stress-induced midbrain lateralization, effortful mental and physical stress tasks evoked proarrhythmic changes in TWR, reflecting increases in local repolarization inhomogeneity and indexed by an increasingly positive TWR value. No significant changes in TWR were observed in patients that did not demonstrate stress-induced right lateralization of midbrain response. A significant group × effort interaction was confirmed. Effortful mental and physical task effects are denoted by the filled bars and effortless control tasks by open bars.

autonomic responses in the periphery. Sympathetic power was significantly correlated with one index of repolarization inhomogeneity, the TCRT, but, at the stringent threshold employed in this study, we were unable to demonstrate the association observed in previous studies (Critchley *et al*., 2003) between cingulate (and insular) cortical activity and efferent sympathetic drive. Thus, further studies are needed to quantify changes in lateralization of cortical and brainstem activity in relation to autonomic responses during stress. In cardiological patients, an alternative hypothesis is that lateralized feedback from an abnormal myocardium biases midbrain centres governing efferent sympathetic autonomic responses. Animal models suggest that abnormalities in efferent–afferent feedback loops may exacerbate proarrhythmic effects (Schwartz *et al*., 1988). However, our observations do not suggest an association with the degree of impaired left ventricular function (Schwartz, 1999) in our patients. Further investigations of interactions between stress and visceral feedback on laterality of autonomic responses may resolve this issue.

Several other aspects of the study require mention. None of the patients developed significant arrhythmia. Increased inhomogeneity of repolarization is the substrate that provides the necessary conditions for arrhythmia, but an additional trigger, such as an appropriately timed ectopic beat, is usually required to initiate an arrhythmia. Our findings are in keeping with those of Lampert and colleagues (2000) who showed that mental arithmetic stress enhanced the inducibility of ventricular arrhythmias triggered by a premature beat induced by programmed electrical stimulation. However, the patients in our study were a heterogeneous group intended to represent a typical cross-section of cardiology out-patients. Several were taking the β-blocking agent atenolol which may have influenced the results, most probably by underestimating the repolarization changes in response to stress. The direct cerebral effects of atenolol are minimal, in contrast to lipophilic β-blockers such as propranolol. Nevertheless, vulnerability to stress-induced arrhythmias spans cardiological diagnostic categories (Zabel *et al*., 2002), and the rigorous characterization of cardiovascular pathology within this group enabled us to demonstrate that the cerebral correlates of proarrhythmic changes in T-wave morphology were not restricted to patients with coronary artery disease.

In summary, our functional imaging observations in patients attending a cardiology clinic provide a unique examination of correlates of cardiac electrical inhomogeneity and cardiac neural control. In particular, these results suggest a link between stress and arrhythmia whereby asymmetrical activation at the level of the midbrain is associated with an asymmetrical neural input to the heart, hence enhancing the repolarization inhomogeneities which predispose to arrhythmias.

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