Heart—brain interactions in cardiac arrhythmia

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ABSTRACT

This review examines current knowledge of the effects of higher brain centres and autonomic control loops on the heart with particular relevance to arrhythmogenesis. There is now substantial evidence that higher brain function (cortex), the brain stem and autonomic nerves affect cardiac electrophysiology and arrhythmia, and that these may function as an interactive system. The roles of mental stress and emotion in arrhythmogenesis and sudden cardiac death are no longer confined to the realms of anecdote. Advances in molecular cardiology have identified cardiac cellular ion channel mutations conferring vulnerability to arrhythmic death at the myocardial level. Indeed, specific channelopathies such as long QT syndrome and Brugada syndrome are selectively sensitive to either sympathetic or vagal stimulation. There is increasing evidence that afferent feedback from the heart to the higher centres may affect efferent input to the heart and modulate the cardiac electrophysiology. The new era of functional neuroimaging has identified the central neural circuitry in this brain-heart axis. Since precipitants of sudden fatal arrhythmia are frequently environmental and behavioural, central pathways translating stress into autonomic effects on the heart might be considered as therapeutic targets. These brain-heart interactions help explain the apparent randomness of sudden cardiac events and provide new insights into future novel therapies to prevent sudden death.

ANGINA OF EMOTION

> '…Every affection of the mind that is attended with either pain or pleasure, hope or fear, is the cause of an agitation whose influence extends to the heart…. A strong man who, having recieved an injury and affront from one more powerful than himself, and upon whom he could not have his revenge, was so overcome with hatred and spite and passion, which he yet communicated to no one, that at last he fell into a strange distemper, suffering from extreme oppression and pain of the heart and breast….'
>
> Exercitatio anatomica de motu cordis et sanguinis in animalibus
>
> W Harvey, Frankfurt-am-Main, 1628

Although recognised in poetry and literature for centuries, the link between the heart and mind has been addressed scientifically only in the past 200 years through anatomical and physiological studies of the autonomic nervous system. Psychologically driven effects on the heart are not necessarily subtle or without significant implications: evidence suggests a causal relationship between autonomic activity and sudden cardiac death (SCD) due to ventricular tachycardia (VT)/ventricular fibrillation (VF).[1–3] The precise mechanisms by which brain activity influences cardiac electrophysiology are now coming to light in the new era of functional neuroimaging and advances in molecular cardiology that link arrhythmogenic mechanisms to mental stress via the autonomic nervous system. These brain—heart interactions help explain the apparent randomness of sudden cardiac events and provide novel insight into future potential therapeutic targets. This review examines what is currently known about the effects of higher brain centres and autonomic control loops on the heart with particular relevance to arrhythmogenesis.

OVERVIEW

Figure 1 presents an overview in which the brain, autonomic nerves and heart are considered as an interactive system. In the brain a number of regions are highlighted that are engaged in autonomic processing. Mental stress or emotion are processed in a network involving these regions, resulting in sympathetic and parasympathetic neural outflow to the heart. Within the heart this neural input exerts a range of modulatory effects including modulating the coronary circulation and electrophysiology.

EVIDENCE THAT HIGHER BRAIN FUNCTION AFFECTS CARDIAC ELECTROPHYSIOLOGY AND ARRHYTHMIAS

Both clinical and experimental observations demonstrate direct influences of higher brain (cortical) activity upon the myocardium and cardiac electrophysiology. This evidence arises from a number of sources.

Acute brain lesions

Myocardial necrosis and stunning

A form of necrosis referred to as cardiac myocytolysis has been demonstrated post-mortem occurring in proximity to intramural nerves rather than blood vessels, and occurring in patients with normal coronary arteries, suggesting a neural origin.[4] One study reported myocytolysis in 26% of non-ischaemic non-cerebral deaths compared with 89% of subarachnoid haemorrhage and 52% of stroke deaths.[5] Myocardial stunning also occurs after stroke and subarachnoid haemorrhage.[6–9]

Autonomic balance

Myocardial damage following stroke may reflect a shift of autonomic balance to sympathetic activity, as evidenced by raised plasma nor epinephrine levels[10–12] and analysis of heart rate variability.[13–15]

ECG changes

Subarachnoid haemorrhage and stroke are associated with higher rates of ECG abnormalities and

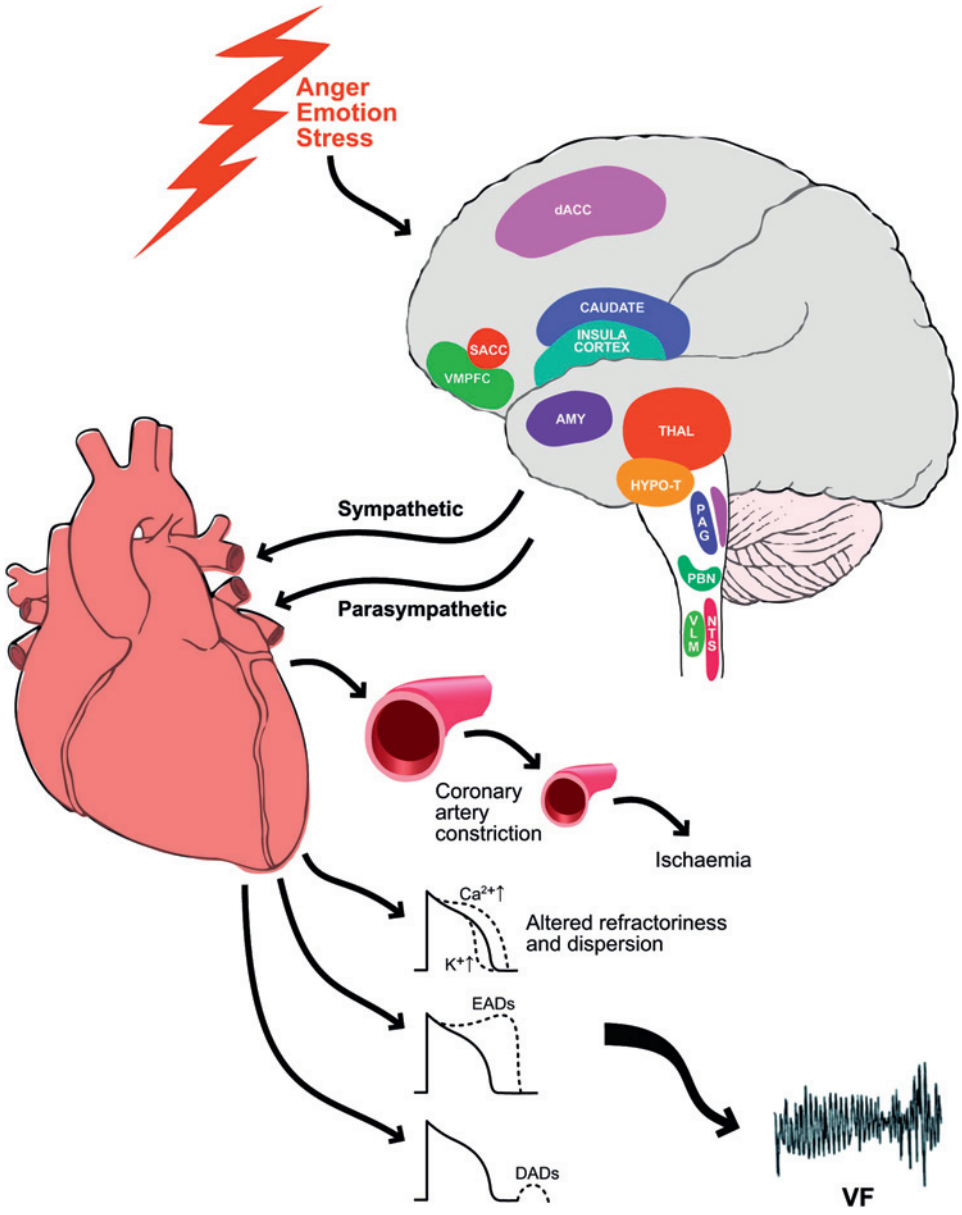

Figure 1 Overview of brain–autonomic nerves and the heart as an interactive system. Brain and brainstem regions are shown concerned with processing mental stress and emotion and with autonomic nerves and reflexes and to the heart. Autonomically mediated effects modulate epicardial coronary artery and microvascular tone and thus myocardial perfusion. Both sympathetic and parasympathetic neural input to the heart influences a number of electrophysiological parameters the result of which includes altered action potential duration and refractoriness, and the generation of early and delayed after-depolarisations. AMY, amygdala; dACC, dorsal anterior cingulate cortex; DAD, delayed after-polarisation; EAD, early after-depolarisation; HYPO-T, hypothalamus; NTS, nucleus tractus solitarius; PAG, periaqueduct grey; PBN, parabrachial nucleus; THAL, thalamus; VF, ventricular fibrillation; VLM, ventrolateral medulla; VMPFC, ventromedial prefrontal cortex.

arrhythmia. ECG changes often resembling myocardial infarction or ischaemia including ST-elevation or depression, deep T-wave inversion and QT prolongation frequently follow subarachnoid haemorrhage and stroke and remain a source of diagnostic misinterpretation.[4 7 16 17]

Arrhythmias

Arrhythmias may follow either acute subarachnoid haemorrhage or stroke.[18–22] The reported incidence of arrhythmias following stroke is understandably higher in studies employing 24 h Holter monitoring compared with ECG recordings. On the basis of ECG recordings, Lavy *et al*[23] reported a 39% incidence of new-onset arrhythmias following stroke in patients with no cardiac history. Goldstein[17] reported a 25% incidence of atrial fibrillation (AF) in acute stroke patients compared with 3% in a control group. A wide range of arrhythmia incidence has been reported from Holter recordings. One study of acute stroke patients reported a 12% overall incidence of ventricular tachyarrhythmias after stroke compared with 3% following a transient ischaemic attack. The respective incidence of ventricular ectopy and AF were 71% versus 73% for ventricular ectopy and 9% versus 3% for AF.[22] In some instances it is difficult to exclude the possibility of AF as a cause rather than the result of stroke. A higher overall incidence has been reported for subarachnoid haemorrhage (89%), with a 29% incidence of non-sustained ventricular tachycardia.[18] In this study arrhythmia incidence correlated with QT interval prolongation but not with cardiac history. Some of the reported effects of subarachnoid haemorrhage and stroke are summarised in table 1.

Epileptic activity

Abnormal brain activity during seizures is associated with abnormalities in cardiac repolarisation, and peri-ictal VT/VF has been reported in the absence of any visible cardiovascular disease.[24] Centrally triggered arrhythmia is the likely cause of sudden unexpected death in epilepsy.

Experimental stimulation of the brain

Focal stimulation of a discrete set of brain regions may produce changes in heart rate, blood pressure, ECG and arrhythmias. In rodents, stimulation of the left insula cortex can induce QT prolongation, ST-depression, marked heart rate slowing, heart

Table 1 Summary of cardiovascular effects of subarachnoid haemorrhage and stroke

Parameter	References
ECG	
ST-depression or elevation	4 7 16 17
T-wave changes	
QT prolongation	
Arrhythmias	11 17–23
Increase in supraventricular and ventricular ectopy, complex ectopy, tachycardia and atrial fibrillation	
Myocardial damage	4–9
Necrosis 'myocytolysis'	
Patchy necrosis around nerve endings myocardial stunning	
Sympathetic activity increased	10–15
Catecholamines increased	
Heart rate variability evidence	

block and asystole,[25] and such experiments suggest hemispheric laterality to be an important factor in cardiac autonomic regulation (see later). In patients undergoing surgery for epilepsy, stimulation of the left insula can induce bradycardia and reduced blood pressure, whereas stimulation of the opposite side increases heart rate and blood pressure. In cats, stimulation of the hypothalamus may produce ECG repolarisation changes,[26] increase sympathetic nerve traffic to the heart and substantially reduce the threshold for electrical induction of ventricular fibrillation. This effect may be prevented by β-adrenergic blockade.[27]

Mental stress

We react both physically and mentally when we are threatened, challenged or put under pressure. Evidence for the association between mental and emotional stress and SCD is increasing. Literature on the topic ranges from anecdotal human observation[28] to controlled experimental studies.[29] Engel[28] described 170 cases in which sudden death occurred within a short time of a stressful emotional event. Rates of SCD measurably increase at the time of national disasters such as earthquakes or missile attacks.[30–32] Both arrhythmia and SCD have a diurnal variation linked to higher morning levels of plasma catecholamines,[33 34] but there is also a Monday morning peak in working individuals, suggesting a relationship to work-related mental stress.[35] Enhanced sympathetic activity appears to be a common intermediary between mental stress and arrhythmia, and vagal stimulation with morphine sulphate has been shown to exert a protective effect against ventricular vulnerability to arrhythmia during psychological stress in a canine model.[36] Chronic psychosocial and socioeconomic factors influence rates of arrhythmia and sudden death[37] and in the laboratory setting, acute experimentally induced mental stress can change heart rate and blood pressure, alter ECG repolarisation and induce arrhythmias.[38–40]

Mental stress in the ischaemic heart

Mental stress may induce ischaemia due to epicardial and/or microvascular constriction.[41–44] Stress-induced sympathetic arousal magnifies the electrophysiological effects of ischaemia. In one canine study, regional ischaemia was induced by occluding a pre-inserted coronary artery snare. When a state of anger/stress was provoked by providing food that was out of reach but accessible to a second dog, ventricular fibrillation developed.[29] In a study in pigs in which regional ischaemia was induced using similar methods, the stress of being raised in a sling resulted in ventricular fibrillation, which could be prevented by surgically interrupting fronto-amygdala pathways in the brain,[45] or the intracerebral administration of centrally acting β-adrenergic blockade.[46] In patients with coronary artery disease, laboratory mental stress tasks and particularly the induction of anger increase the propensity to develop ECG repolarisation alternans,[47 48] a recognised risk factor and predictor of ventricular arrhythmias and SCD.[49–51]

Ultimately these findings provide support for the notion that psychological stress may evoke ECG changes, arrhythmias and SCD though specific central neural and peripheral autonomic pathways (table 2).

Mental and emotional stress and the brain

Mental and emotional stress is expressed in the brain as changes in the activity of a subset of brain regions, including the insular cortex (the insula), cingulate cortex and amygdala.[52] These regions encapsulate what was implied in the term 'limbic system', as interfaces between emotional feeling states engendered by our external environment and social interactions and visceral responses of the body that guide and facilitate our motivational behaviour. The insula, buried deep between temporal and frontal lobes, can be viewed as the viscerosensory cortex, the terminus of interoceptive pathways from the viscera relayed via the ventromedial thalamus and containing within it the taste cortex.[53 54] The cingulate cortex (hugging the corpus callosum in each hemisphere), associated with quite complex thinking processes, can also be considered as the visceromotor cortex, particularly in anterior regions, where neuroimaging has highlighted contrasting/complementary roles of the dorsal and ventral regions in attentional engagement and autonomic arousal. The amygdala is important in detecting and learning threat even in the absence of conscious awareness. These closely connected brain regions are now viewed together as a 'salience network', acting on frontal, temporal and striatal centres to shape our thoughts and behaviours and directly on hypothalamic and brainstem centres to change our bodily arousal state through direct coupling with sympathetic and parasympathetic efferent nuclei and feedback control loop.

EVIDENCE THAT BRAIN STEM AND AUTONOMIC NERVES AFFECT CARDIAC ELECTROPHYSIOLOGY AND ARRHYTHMIAS

Autonomic nerves

In general, stimulation of the sympathetic limb of the autonomic nerves is pro-arrhythmic in the ventricle, whereas the parasympathetic limb is protective. Experimental stimulation of sympathetic nerves or stellate ganglia induces ECG repolarisation changes and reduces the fibrillation theshold, ie, facilitates VF initiation.[55–57] On the other hand, β-adrenergic blocking agents can improve survival in patients following myocardial infarction, implying an important role of sympathetic tone in VT/VF and SCD.[58 59]

Brainstem reflexes

Central inhibition of the sympathetic drive using clonidine will reduce the occurence of VT/VF in a canine heart failure model.[60] Sympathetic and parasympathetic nerve traffic between brainstem and heart is modulated by reflex mechanisms.[61]

The baroreflex

Pressure and volume changes alter the firing of stretch-sensitive neurons located in the adventitia of arteries, particularly the

Table 2 Summary of evidence for a role of mental stress in arrhythmias and sudden death

Model	Evidence	References
Anecdotal reports	Anecdotal reports from modern to ancient times	28
National disasters	SCD increases at times of national disasters	30–32
Experimental models in animals	Vagal stimulation protects against stress-induced arrhythmia in dogs	36
	Stress magnifies the pro-arrhythmic effects of ischaemia	29
	Fronto-amygdala brain section prevents stress-induced VF	45
	Central acting β-blockers prevent stress-induced VF	46
Humans	Stress induces coronary or microvascular constriction and ischaemia	41–44
	Stress tasks and anger induce ECG T-wave alternans	47 48
	Anger potentiates ventricular arrhythmias	38
	β-Blockade protective for SCD	3
	Emotion precipitates VF in long QT patients	3
Socioeconomic influence	Chronic psychsocial factors inflence rates of arrhythmia and sudden death	37

SCD, sudden cardiac death; VF, ventricular fibrillation.

aortic arch and the carotid arteries. An increase in aortic pressure/volume thereby triggers afferent baroreceptor impulses to the medulla. This in turn results in decreased efferent sympathetc and increased efferent parasympathetic activity in order to restore pressure homeostasis.[62] The functioning (sensitivity) of this baroreflex is depressed by stress[63] and enhanced by relaxation and controlled breathing.[64] Baroreflex sensitivity is also depressed in patients after myocardial infarction and with cardiac failure. Depressed baroreflex sensitivity is a risk factor for arrhythmia and sudden death in both animal models[65] and in patients.[66] Heart rate turbulence, which uses the transient haemodynamic perturbation following a premature beat to derive an ECG index relating to baroreflex function, is also a powerful risk indicator.[67 68] Here several mechanisms may be operative through the brainstem baroreflex, for example transient hypotension following the onset of tachyarrhythmia, if not restored quickly on account of a depressed baroreflex, may result in ischaemia in diseased hearts.

Cardio–cardiac reflexes

Stimulation of sensory nerve endings in the heart may induce powerful haemodynamic effects. Afferents located in the inferior and posterior left ventricular wall activated by chemical agents or possibly stretch also relay through the vagus to the brainstem and evoke efferent vagal activity, which induces bradycardia (the Bezold–Jarisch reflex),[61 69] a possible mechanism of syncope in patients with aortic stenosis. An increased incidence of bradyarrhythmias with hypotension occurs in patients with inferior compared with anterior infarction. Stimulaton of the anterior wall may produce a sympatho-excitatory response through brainstem-mediated reflexive responses.[70]

Sympathetic nerve damage: 'nerve sprouting'

Myocardial ischaemia or infarction is known to damage sympathetic nerves resulting in distal regions that are denervated and hypersensitive to circulating catecholamines (denervation hypersensitivity). Nerve regrowth may then occur from the proximal ends resulting in patchy hyperinnervated regions.[71–75] The local increase in sympathetic neurotransmitters is thought to result in electrical remodelling with increased calcium and decreased potassium ion current densities,[76] action potential duration (APD) prolongation and the potential for calcium overload and triggered activity. The juxtaposition of normally innervated, hyperinnervated and denervated regions therefore presents a highly pro-arrhythmic substrate. Studies in animal models in which spatially heterogeneous overgrowth of cadiac sympathetic nerve fibres was induced showed a dramatic increase in the incidence of SCD from VT/VF.[72 77]

Enhanced sympathetic activity as a precursor of VT and SCD

Clinical studies using the spectral power of the oscillatory behaviour of interbeat heart rate intervals to index parasympathetic and sympathetic influences on the sinus node (heart rate variability) suggest increased sympathetic and/or decreased parasympathetic activity immediately preceding the onset of VT. Shusterman and colleagues[51] reported an increase in sympathetic activity in the 30 min before the onset of ventricular tachyarrhythmias in patients with ischaemic heart disease on the basis of an increase in heart rate and changes in the spectral power of heart rate variability. β-Adrenergic blockade exerted a protective effect.

The intrinsic cardiac nerves

The sympathetic and parasympathetic nerves in the mediastinum converge to form a highly complex neuronal network in and around the heart consisting of more than 94 000 neurons in young hearts and 43 000 in adult ones both of humans and dogs[78 79] (figure 2). In humans as well as in examined animal models seven ganglionated subplexuxes are located at specific epicardial sites consistent from heart to heart. This intrinsic nervous system is thought to be able to function independently and fulfil a number of important interactive and modulatory functions including modulation of the arrhythmia substrate.[80] Although a great deal has already been learnt clearly this in an important aspect of autonomic control in need of further work, and is particularly pertinent to AF as discussed below.

Autonomics and AF

Coumel *et al*[81] originally described the role of the autonomic nervous system in the initiation of AF in the 1970s. Indeed,

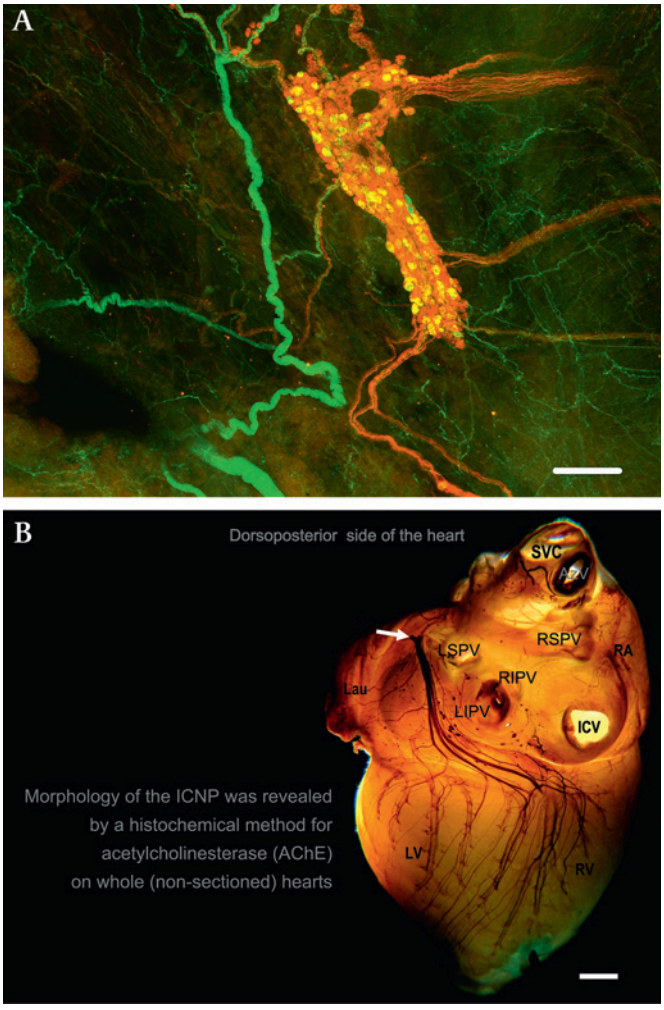

Figure 2 Intrinsic cardiac nervous system. (A) Microphotograph of immunohistochemical simultaneous staining of choline acetyltransferase (ChAT) and tyrosine hydroxylase (TH) on a whole-mount preparation of the mouse left atrium to demonstrate the different pathways of parasympathetic (ChAT-positive, seen in red) and sympathetic (TH-positive, seen in green) nerves. Note the parasympathetic nerve fibres (red) extending mostly to and presumably from the ganglion that contains abundant neurons immunoreactive to ChAT (red), TH (green) as well as both to ChAT and TH (yellow). Scale bar 200 μm. (B) Photomacrograph of the dorsoposterior side of the 1-month-old canine heart illustrate the location, course and extent (capacity) of the left dorsal neural ganglionated plexus revealed on the total heart employing histochemical staining for acetylcholiesterase. Note the high concentration of epicardial ganglionated nerves inside the Marschall ligament on the left atrium that massively proceed forward of the coronary sinus and to ventricular coronary blood vessels. Epicardail ganglia are seen as dark differently sized spots along the stained nerves. The arrow points to the site where the extrinsic cardiac nerves are reflected onto the heart and subsequently course epicardially as the left dorsal ganglionated nerve subplexus. AzV, root of the azygos vein; ICV, orifice of the inferior vena cava; Lau, left auricle; LIPV, root of the left inferior pulmonary vein; LSPV, root of the left superior pulmonary vein; LV, left ventricle; RA, right atrium; RIPV, root of the right inferior pulmonary vein; RSPV, root of the right superior pulmonary vein; RV, right ventricle; SVC, root of the superior vena cava. Scale bar 2 mm. Illustrations from Professor Dainius Pauza.

increased vagal tone during sleep is recognised as a trigger in young patients without structural heart disease while increased sympathetic tone is more relevant in patients with other cardiac pathology or after cardiac surgery. The complex autonomic network of ganglionated plexi surrounding the heart has recently been implicated in both the triggering and maintenance of AF. Elegant anatomical studies of the vagal and sympathetic fibres surrounding the atria demonstrate dense networks of fibres particularly at the pulmonary vein ostia, which are recognised as critical triggers in paroxysmal AF.[82] In ambulatory canine models, simultaneous sympathovagal discharges (rather than isolated sympathetic activation) are typical triggers of paroxysmal atrial tachycardia and AF.[83 84] This occurs since late phase 3 early after-depolarisations (EAD) are induced due to the coexistence of increased amplitude and duration of intracellular calcium transient and the shortened APD. Vagal stimulation shortens APD and therefore is needed to promote late phase 3 EAD.[85 86] This promotes local atrial ectopy, and due to the marked anisotropy of myocardial fibres in the pulmonary vein ostia and antra local re-entrant circuits can be maintained to perpetuate AF.

Autonomics and ablation techniques

Current ablation techniques focus upon pulmonary vein isolation as the endpoint of the procedure, although it is conceivable that denervation of the ostia independent of pulmonary vein electrical isolation may be just as significant, especially when one considers the fact that pulmonary vein reconnection rates in patients free of AF post-pulmonary vein isolation are equivalent to those with recurrences[87] revealing that other effects of ablation are operative. Stimulation of these ganglionic plexi can induce AF.[88] Furthermore, ablation of pulmonary veins is associated with a bradycardic response indicating vagal stimulation during ablation. There has been interest in ganglionic plexi ablation as a strategy to improve AF ablation outcomes because ablating these plexi may prolong the local atrial refractory periods and abolish the ability to induce AF during pulmonary vein stimulation. Ganglion ablation has been suggested to result in the preservation of sinus rhythm in as many as 50–84% of patients over a short follow-up period and may result in fewer recurrences of AF, especially when ablation is performed in areas that elicit marked vagal responses.[89] Therefore, this neural network of autonomic plexi have an important influence on atrial arrhythmogenesis and demonstrate that complex neural inputs can influence the electrophysiology of the atria and pulmonary veins.

THE ROLE OF THE HEART

Dynamic interactive substrate

The majority of serious ventricular arrhythmias and VF arrests occur in people with cardiac pathology, usually coronary artery disease.[90] Conventional wisdom requires a trigger and the presence of a substrate such as hypertrophy, fibrosis, an anatomical scar and ischaemia. However, recent studies highlight the dynamic nature of this substrate due to constantly changing electrophysiological properties that partly reflect fluctuations in autonomic nerve balance. For example, sympathetic nerve activity strongly influences major components of arrhythmogenesis, namely automaticity, after-depolarisations, ventricular and atrial APD and refractoriness, APD restitution,[91 92] conduction velocity and dispersion of repolarisation. Sympathetic effects on repolarisation and refractoriness are magnified in the presence of ischaemia.[93 94] The magnitude of beat-to-beat repolarisation (T-wave) alternans, a common precursor of VF, is enhanced by increased sympathetic activity and reduced by β-blockade.[95] This variability in repolarisation creates the optimal mileu for lethal arrhythmia in the substrate. However, in addition to this, a trigger such as a ventricular ectopic beat is necessary to initiate VT or VF. Such triggers have been described in idiopathic VF and may be eliminated through ablation if

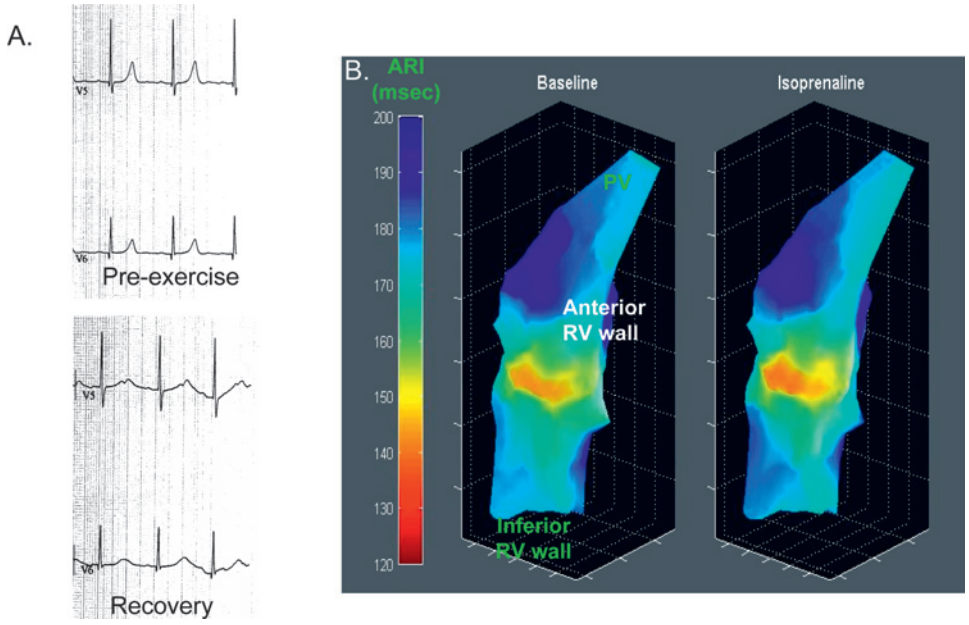

Figure 3 Surface ECG and endocardial effects of adrenergic stress on repolarisatioon in long QT and normal hearts. (A) In Long QT syndrome adrenergic stress of exercise promotes marked QT prolongation leading to a bifid T-wave in recovery from exercise. (B) Effects of isoprenaline on endocardial activation recovery intervals (ARI) in the normal right ventricle (anteroposterior view) recorded by non-contact mapping during pacing the right ventricle (RV) apex at 400 ms cycle length in steady state. Note that isoprenaline shortens ARI particularly in the mid-anterior RV wall. Pulmonary valve (PV) in this normal RV.

consistently arising from the Purkinje network.[96] Autonomic activity influences the development of these triggers.

Genetic predisposition

The pathological repolarisation effects of specific ion channel disorders such as long QT and Brugada syndrome are directly influenced by the autonomic nervous system. These effects are not solely related to the behaviour of the ion channel in response to epinephrine/Ach but also the intrinsic activity of the autonomic nerves:

Increased sympathetic drive is pro-arrhythmic in long QT 1 and 2

SCD is more common under conditions of increased anxiety (and during exercise) in the two subtypes of long QT syndrome. Enhanced sympathetic activity can substantially increase spontaneous inward current through L-type calcium ion channels to increase the likelihood of EAD. Clinical data indicate that carriers of mutations in either KCNQ1 or KCNE1 are at increased risk of experiencing fatal arrhythmias in the context of elevated sympathetic activity. In long QT subtypes 1 and 2, increased adrenergic tone prolongs the QT interval at peak exercise and in early recovery (figure 3A). This is opposite to the normal response of QT shortening on exercise and reduced endocardial repolarisation times (figure 3B) in conditions of increased adrenergic stress. More recently, an adaptor protein, yotiao, was found to couple to the C-terminal of the KCNQ1/KCNE1 complex and bind to the regulatory enzymes protein kinase A and protein phosphatase 1, which are upregulated by adrenergic β-receptor stimulation.[97] Therefore, this channel complex, through the adaptor protein, recruits enzymes that can upregulate and downregulate channel activity. When this molecular complex is disrupted, the channel is disregulated, compromising the control of the action potential in the ventricle, thereby increasing the risk of arrhythmias. This may manifest as APD prolongation, epicardial alternans and failed reduction in APD at short coupling intervals; each of which is highly arrhythmogenic. Genotype can also influence risk, with mutations for long QT 1 and 2 affecting the pore-forming region carrying the highest risk. In long QT 1 a reduced gating frequency of the slow component of the delayed rectifier potassium current (Iks) during conditions of increased adrenergic tone may explain the failure of APD and QTc to shorten during exercise and thus promote regional heterogeneities in APD and thus VT/VF.

Another link between long QT syndrome and the sympathetic nervous system is disclosed by a recent study showing that ERG genes are expressed in chromaffin cells, especially adrenaline-containing cells, and sustain a potassium ion current.[98] Blockers of ERG channels modify the excitability of single chromaffin cells and increase the release of catecholamine-amplifying repolarisation changes in long QT under conditions of increased emotional stress.

Schwartz *et al*[99] recently demonstrated that baroreceptor sensitivity and heart rate variability predict a higher risk of clinical events in a certain form of long QT 1 due to the expression of two polymorphisms that enhance adrenergic activity. The ADRA2C-Del322-325 polymorphism causes reduced function of an α2 adrenergic receptor, which in turn enhances norepinephrine release by reducing inhibitory feedback.[100] The ADRB1-G389R polymorphism enhances coupling of the β1 adrenergic receptor to adenylate cyclase and augments adrenergic stimulation.[101] Correlations between these polymorphisms and baroreceptor sensitivity are intriguing and support the inference that higher baroreceptor sensitivity reflects higher sympathetic tone. Variations in autonomic tone can thus directly affect myocardial electrophysiology in long QT and these may be exaggerated by changes in emotional state.

The effect of increased vagal tone in long QT 3 and Brugada syndrome

Increased vagal tone can also promote ventricular tachyarrhythmia in defined arrhythmic syndromes associated with cardiac sodium channel mutations namely long QT 3 syndrome and Brugada syndrome.[102 103] In Brugada syndrome the dynamic changes in J-point elevation and ventricular arrhythmia are induced by increased vagal tone.[104] Nakazawa *et al*[105] reported that high vagal tone and low sympathetic tone are specific properties of symptomatic Brugada syndrome by analysis of heart rate variability using Holter ECG recordings. Their findings suggested that these autonomic imbalances were significant in the symptomatic group but not in the asymptomatic group. Dynamic changes in J-point elevation are more prominent at

night particularly in patients with previous VF consistent with sympathetic dysfunction shifting autonomic balance with an increase in cholinergic tone. A recent study demonstrated abnormal 1231-MIBG uptake in patients with Brugada syndrome indicating abnormal presynaptic noradrenaline recycling.[106] The precise relationship between vagal tone and arrhythmic vulnerability is subject to debate. Increased vagal tone is thought to reduce the calcium transient during phase 2 of the action potential resulting in increased transmural dispersion of repolarisation and phase 2 re-entry.

Although long QT and Brugada syndrome are rare disorders with a prevelance of 1:5000 to 1:10 000 of the population, they illustrate that mutations in specific ion channel genes can increase the susceptibility of the myocardium to changes in autonomic tone. This susceptibility may be more exaggerated in these disorders, but such changes may be pronounced in individuals with specific ion channel polymorphisms, which downregulate channel function in a more subtle way, particularly if a number of such polymorphisms in one individual interact to generate a more pro-arrhythmic substrate. The importance of vagal tone in SCD has been further highlighted by the link between infero-lateral J-waves and both primary VF and increased cardiovascular mortality. These J-waves become more exaggerated in conditions of high vagal tone in a similar manner to Brugada syndrome, indicating that high vagal tone may be pro-arrhythmic in other substrates other than Brugada and long QT. Variations in G protein coupling may also play an important role in amplifying the response to cholinergic tone and thus the susceptibility of the substrate to neural input. Indeed, these observations suggest that just as autonomic tone has a genetic influence so should the patterning of synaptic activity and neural–cardiac interconnections. Beyond these relatively rare genetic disorders, more general genetic vulnerabilities to cardiac arrhythmia are suggested by the strong female preponderance of patients with Takotsubo cardiomyopathy,[107 108] in which emotional stress induces apical hypokinesia and ballooning, thought to be temporary stunning due to regional hypersensitiviy to catecholamines.[109]

Laterality hypothesis

One suggested mechanism by which mental stress triggers arrhythmia is known as the 'laterality hypothesis', in which lateralised imbalance of autonomic neural drive to the heart may enhance pre-existing electrical inhomogeneity thereby favouring the initiation of re-entrant arrhythmias.[110] While proof of this hypothesis is awaited, there is evidence in support of its components. The left-sided sympathetic nerves have been shown both functionally and anatomically to be distributed predominantly over the postero-inferior aspect of the ventricles and the right-sided nerves predominantly over the anterior aspect of the ventricles, albeit with considerable overlap and variability [55 111 112] and with an anastomotic network in the form the intrinsic cardiac nervous system around the heart.[78 79 113] There is anatomical evidence for ipsilateral channelling of neural activity from brainstem regions to the autonomic nerves.[53] Stimulation studies in humans suggest lateralisation of efferent sympathetic pathways below the cortex, with segregation of left and right responses maintained at the level of the brainstem and spinal cord.[114] At the level of the cerebral cortex, evidence from clinical studies and positron emission tomography neuroimaging experiments suggests cortical regions in the right hemisphere, particularly the right insula and anterior cingulate cortices, are particularly involved in the generation of sympathetic responses.[115–117] There is also a body of evidence suggesting differential hemispheric contributions to the processing of stress and negative emotion; for example,[118 119] when negative emotional challenges activate regions in the right more than left hemisphere. There is not universal acceptance of this model, yet a 'visceral' basis to emotional brain lateralisation has been proposed.[118] Perhaps not everyone shows this hemispheric bias in emotional brain responses. Nevertheless, mental stress alters repolarisation, even in healthy people perhaps representing

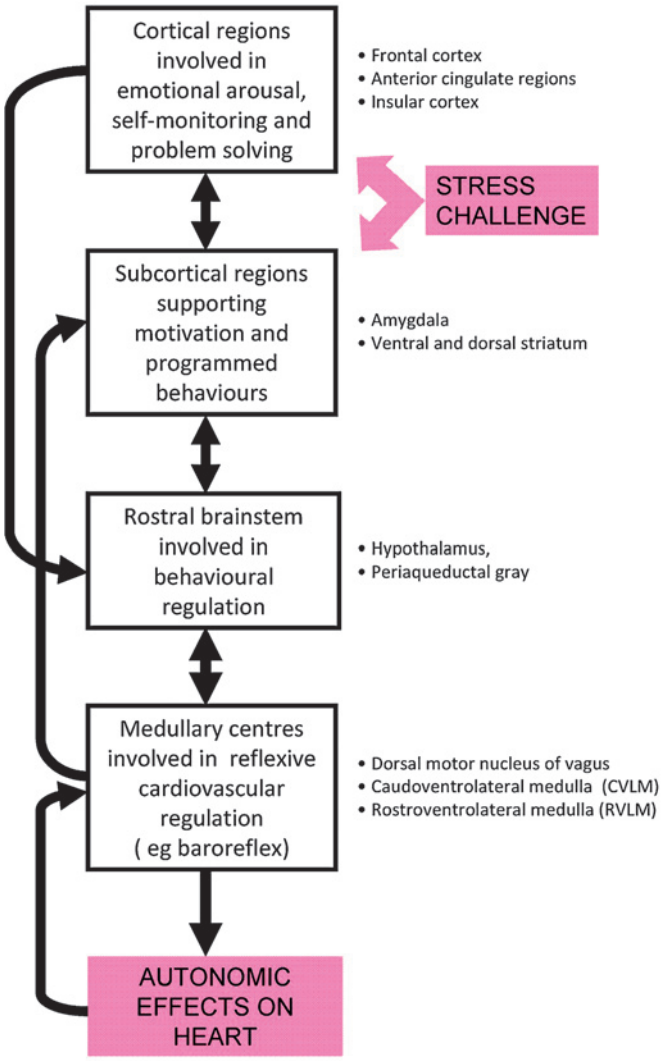

Figure 4 Brain circuitry contributing to arrhythmogenesis. Emotions represent action programmes in response to events of evolutionary importance and that are expressed as feeling states, behaviour and autonomic responses (affecting the heart). The response to stress can be automatic generating rapid 'fight or flight' autonomic reactions automatically through subcortical centres (that hold preset physiological and behavioural programmes), yet both acute and chronic stress can arise through cognitive processes supported in frontal, cingulate and insula cortices that reflect the conscious appraisal and realisation of the significance of events, whereby thoughts evoke powerful emotional states that impact on cardiovascular control. The figure illustrates the cortical 'high road' and subcortical 'low road' to emotions. Laterality in the cortex is relevant (see text, with the weight of evidence suggesting that arrhythmogenesis in humans is associated more with engagement of the non-linguistic 'emotional' right hemisphere). Critical in the pathways between mental states and autonomic effects on the heart is the rostral brainstem, containing centres for complex homeostasis that impact directly on thinking and feeling and that regulate homoeostatic reflexes such as the baroreflex expressed through sympathetic and parasympathetic efferents to the heart. These functional relationships between these systems are illustrated.

a descending overspill from asymmetrical cortical activity during emotional processing.[110]

Evidence that feedback from the heart to higher centres affects cardiac electrophysiology and arrhythmias

An afferent–efferent loop in cardiac autonomic control exists such that, in health, feedback from the heart regulates the efferent autonomic drive as described above for the baroreflex. In patients with ischaemic heart disease, feedback from an abnormal heart may exacerbate pro-arrhythmic efferent autonomic drive. In a positron emission tomography study, changes in regional brain activity induced by mental and physical stress (mental and exercise pressor tasks) were correlated to pro-arrhythmic changes in cardiac repolarisation in patients with heart disease.[120] In particular, stress tasks enhanced sympathetic drive to the heart and evoked pro-arrhythmic changes on ECG correlated with a right-lateralised shift in dorsal pons and midbrain activity. Moreover, this right lateralisation predicted the extent to which pro-arrhythmic changes occurred and which patients were at greatest risk. These findings were consistent with lateralisation of efferent autonomic drive at the level of a brainstem relay to the heart, endorsing the model of acute cardiac pathology from lateralised overspill of stress-related cortical activity. However, the study did not exclude the role of the presence of pre-existing cardiac disease as an amplifying factor through central afferent feedback of abnormal cardiac responses. This notion was examined in an electroencephalographic study. A signature of afferent cardiac activity (a heart beat-evoked potential) was identified that reflected the integrity of effective cardiac function. Changes in this measure were examined during mental arithmetic in cardiac patients who varied in the degree to which they could mount an effective cardiac output response to the stress challenge.[121] These observations suggest that, even in cortical brain regions, interaction between feedback from an abnormal heart and the generation of arrhythmia is expressed dynamically, with implications for understanding brain mechanisms of stress-induced SCD.

Progress in identifying the circuitry

Ultimately there is no single arrhythmogenic centre in the brain, rather a network of structures which, in health, balance homoeostatic needs with the control of cardiovascular responses to meet (real or anticipated) behavioural demands. Cardiac arrhythmia can thus have neural origins at multiple levels within the brain (figure 4). Specific brain regions couple the experience of stress and negative emotion to sympathetic drive. In the medial hemispheric surface of the frontal lobe, the anterior cingulate cortex is strongly implicated in efferent cardiovascular drive through dorsal anterior cingulate activation and ventral anterior cingulate deactivation (the latter is potentially more closely linked to parasympathetic function).[52 120 122 123] The insula cortex (mentioned earlier) is increasingly viewed as part of the same emotional/autonomic control system as anterior cingulate cortices, although its role appears to be more viscerosensory than visceromotor (figure 5). Among subcortical structures, amygdala activity is important in initiating bradycardia responses to acute fear, and predicting increased ventricular filling during stress.[124] Links between amygdala function and sympathetic skin response are established.[125–127] However, in some experimental studies amygdala activity is associated with cardiovascular acceleration,[120] while other studies show negative or no correlations with heart rate.[117 122 123 128] Basal ganglia structures (caudate–putamen complex) are involved in motor behaviour and understandably also play a 'contextual' role in autonomic drive to the heart. Caudate activity is related to heart rate and heart rate variability in social stress, and can be strongly evoked by symptom provocation in anxiety patients.[122 123 129] Moreover, in syncopal individuals, the structural integrity of the caudate nucleus reflects the interaction between anxiety, parasympathetic tone and fainting frequency.[130] Within the brainstem, functional neuroimaging studies highlight the role of the periaqueductal grey matter (PAG) as a relay in mediating stress and heart responses to physiological[131] and psychological challenges.[122 123] The PAG, with the amygdala and insula, provides a site of integration of afferent and efferent autonomic control, where baroreceptor feedback and individual parasympathetic tone alters efferent sympathetic responses to the cardiovascular system.[132 133] Anatomically, the PAG is connected reciprocally to insula, amygdala and medulla centres involved in the baroreflex.[134–136] In animals, the link between efferent and afferent autonomic control of the heart is traceable in the lower brainstem, including the medulla and the interplay between the nucleus of the solitary tract. Activity from baroreceptors, beginning at the upstroke of each pressure wave, is relayed via the nucleus of the solitary tract to the caudal ventrolateral medulla. From there, inhibitory projections dampen descending sympatho-excitatory efferent outputs generated within the

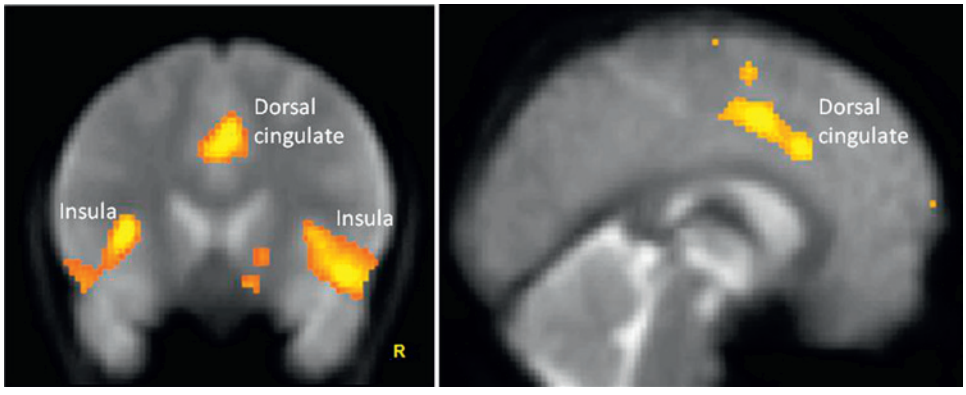

Figure 5 Brain activity correlating with task induced changes in low frequency heart rate variability. Group data are shown on coronal (left showing dorsal cingulate and bilateral insular cortical activity) and parasagittal (right showing mid to anterior cingulate activity) sections of a group mean functional magnetic resonance brain image. Healthy participants were scanned while performing handgrip exercise and mental stress (working memory) tasks at two levels of difficulty during brain scanning with ECG. Measures of heart rate variability were derived and regressed against regional changes in brain activity, controlling for all other aspects of task performance and confounds including movement.[52]

rostral ventrolateral medulla.[137] Neurons within the caudal ventrolateral medulla exhibit tight cardiac synchrony and reflect arterial blood pressure at each cardiac cycle.[138] Increasingly sophisticated human imaging studies, measuring directly sympathetic nerve traffic in muscle fibres, link activity increases within the medulla, insula, hypothalamus and anterior cingulate to efferent sympathetic drive.[139]

In summary, imaging studies in humans of pro-arrhythmic changes in the heart implicate a specific set of subcortical and cortical brain regions. Key among these are the dorsal and subgenual regions of the anterior cingulate cortex, insula cortex (where dominance of right lateralisation of response may accompany negative emotional processing) and to a lesser extend the amygdala and basal ganglia. Brainstem regions including the PAG and parabrachial nucleus shape descending drive to the heart through the integration of afferent baro/mechanoreceptor information.

Therapeutic implications and opportunities for novel pharmacological intervention

Anti-arrhythmic drugs typically focus on direct effects on the heart, yet because precipitants of sudden fatal arrhythmia are environmental and behavioural, then central pathways translating stress into autonomic effects on the heart should be considered as therapeutic targets. Although cervical sympathectomy has been shown to reduce lethal arrhythmia in long QT and catecholaminergic polymorphic ventricular tachycardia, this only targets the terminal end of the sympathetic efferents to the heart. A more sophisticated approach to the central command of cardiac autonomic tone may be of benefit and provide more positive subtle effects.

The role of sympathetic adrenergic activity on arrhythmogenesis and the beneficial effects of β-adrenoreceptor blockade extend to effects on the brain. Lipophilic β-blockers such as propranolol act centrally and impact on emotional as well as physiological responses. Lipophilic β blockers such as propranalol and nadolol were the first β blocker agents to be used to treat long QT syndrome. They may exert additional protective effects compared with more selective β1 agents (eg, atenolol) in long QT syndrome both by the fact that they antagonise both β1 and β2 receptors and may have additional central effects to reduce sympathetic tone further centrally. There is some evidence to suggest that in a small series examining β-blocker failures,[140] event rates were higher in the atenolol group in compliant patients. However, the high quality clinical data needed to address this specific issue are limited as non-compliance with β-blockade is also a significant factor in β-blocker failure.

One target of β-blockade is on the emotional memory in which strong emotions linked to high autonomic arousal produce strong memories through the central release of norepinephrine in medial temporal regions. The strength of these memories can be modified by β-blockade at the time of the event or, interestingly, when given during subsequent recollection of the event (now a potential means of augmenting psychological therapies).[141]

Identifying specific brain centres underlying cardiac risk can suggest new therapeutic targets. The dorsal anterior cingulate/insula system has distinct neural architecture including clusters of large pyramidal cells (von Economo neurons) whose function may relate to cardiac control.[141 142] The anterior cingulate cortex is also rich in (μ)-opioid receptors implicated in autonomic and psychological responses to pain. The 'interoceptive' insula cortex and hypothalamus express distinct neuromodulator (eg, 5-hydroxytryptamine 5-HT subtypes) and peptide receptors, providing further potential targets that may impact on stress-mediated arrhythmogenesis. Notably, the central action of a tetrapeptide of cholecystokinin is particularly associated with emotional arousal and panic,[143] while the central action of oxytoxin is linked to positive (affiliative) reductions in stress.[144] The central effects of antidepressants and antipsychotics mediate a shift to sympathetic/parasympathetic balance in heart rate variability in psychiatry patients,[145 146] and more direct pro-arrhythmic changes (eg, QT prolongation). Within psychopharmacology for neurological and psychiatric conditions there is much interest in neural growth factors, central cytokine production and related systems, these undoubtedly play a role in stress responsivity and its cardiopathological expression. New physical interventions may also have something to offer to the management of arrhythmogenesis. Deep brain stimulation, a reversible neurosurgical technique, for example, can attenuate seizures and therefore seizure-induced autonomic effects on the heart. There is active interest in deep brain stimulation, targeting PAG, in relation to cardiovascular control.[147] As knowledge increases about the anatomy of brain–heart interaction, deep brain stimulation may be applied to abort arrhythmia. Finally, psychological therapies play a role: a cognitive-behavioural management programme has been developed at the National Refractory Angina Centre, which significantly improves angina and quality of life and has reduced admissions and infarction rates.[148 149]

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