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Chapter 6

Interaction between cognition, emotion, and the autonomic nervous system

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INTRODUCTION

Autonomic control is integrated with cognition and emotion. The expression of advanced cognitive capabilities in humans, involving consciousness and language alongside a rich repertoire of emotions within complex social environments, ultimately arises through evolutionary imperatives determined through selective pressure to survive and reproduce. Homeostatic control, to which the autonomic nervous system is crucial, maintains the basics for physical survival. Social and emotional behavior is thus shaped by environmental challenges in the context of homeostatic needs. Superordinate cognitive processes are also subject to these influences. Brain and body are intrinsically and dynamically coupled; perceptions, emotions, and cognitions respond to, and change, the state of the body. These interactions form much of the content of psychophysiological research identifying bodily signatures of mental activity.

The concept of arousal is interesting in this regard, referring to mental sharpening that enhances attention to, and the processing of, potentially important information (salience is a term for this potential motivational importance). Arousal can improve the performance of effortful tasks. Arousal is also used to refer to physical states of action-readiness often identified through autonomic signatures such as changes in sympathetic skin response. In many instances, these psychological and peripheral physiological concepts of arousal overlap, as in coma and wakefulness or the attentional orienting and sympathetic reaction ("fight or flight response") elicited by an unexpected loud sound. However, the general notion of arousal, when applied to autonomic function, underplays the precision of autonomic control expressed through detailed organ specificity and patterning of visceral responses. Moreover, there are relatively common occasions when physiological preparedness (or the related concept, "activation") and psychological alertness dissociate: examples include disinhibiting effects of sedative drugs, exaggerated startle responses in delirium, or conversely, the physiological calm necessary to undertake demanding mental tasks (e.g., as demonstrated by the detrimental effects of stress-related arousal on working memory) (Schoofs et al., 2008).

Neuroimaging in humans can provide mechanistic insight into interactions between cognition, emotion and the autonomic nervous system. Functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) allow regional changes in brain function (via proxies in local cerebral hemodynamics) to be related to perception, thinking, and feeling. Once concerns are managed regarding the potentially confounding nature of autonomically mediated changes in physiological state on regional hemodynamic signals of brain neural activity, the combination of functional neuroimaging with autonomic monitoring provides novel and clinically relevant data. This chapter draws together evidence in humans for the integration of autonomic nervous control with cognition and emotion, highlighting clinical implications. It is an attempt to illustrate principles rather than comprehensively summarize the field.

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AUTONOMIC INTERACTION WITH COGNITION AND EMOTION

Perceptions, cognitions and emotions interact with autonomic nervous control in specific ways and at different levels of the neuraxis:

1. Mental processes influence autonomic responses to alter the physical state of the body. This can occur: (i) directly and automatically through autonomic nerves; (ii) indirectly though changes in respiration, skeletomotor activity or posture under partial or full volitional control; or (iii), as intentional or incidental consequences of enacting behavioral decisions.
2. The internal physiological state of the body can influence mental processes. Thus: (i) sensory representation of the internal bodily state can grab attention, compete for representational or cognitive resources, and interrupt ongoing thoughts and feelings; (ii) information arising from the body may also be fully integrated with perceptions and cognitions, potentially adding to impact, for example, arousal will enhance encoding into memory; (iii) autonomic/visceral state acts as a variable context (e.g., "occasion setter") (Bouton, 1993; Bouton et al., 2001) for emotional and cognitive processes, for example, information learned in low arousal is best recalled in low arousal.
3. The central interaction of processes supporting the generation and the representation of autonomically mediated changes in visceral state may be the critical mediator of autonomic influences on cognition and emotion. Central viscerosensory and visceromotor representations are exchanged as afference and efference copies to allow error signaling. Where there is mismatch between intended and actual autonomic state, corrective efferent reactions are accompanied by interpretative processes. The unconscious operation of the autonomic nervous system can be interrupted by deviations from expected state, i.e., we become aware of our autonomic bodily state when we experience changes in internal state that are "unpredicted" by control centers.

AUTONOMIC INTEGRATION AND INTERACTION WITH COGNITIVE PROCESSES

Autonomic interaction with engagement, attention, cognitive and mental effort

Engagement with stimuli in the environment engenders a distinct state of body and of mind, characterized by psychological and physiological arousal and reactivity. These changes are a focus of much psychophysiological research (including autonomic, electroencephalographic and neuroimaging studies) that attempts to understand this basic level of mind–body integration. Here we focus on neuroimaging data.

Almost from the outset, functional imaging studies of human brain revealed increased activity in dorsal anterior cingulate cortex (dACC) when people are engaged in cognitively demanding tasks. A typical "cognitive activation" neuroimaging experiment (notably those using $H_2{}^{15}O$ PET), would contrast performance of a task containing the cognitive process of interest with a control task that was similar in terms of sensorimotor performance but lacked the extra cognitive element. For example, performing a mathematical puzzle would be contrasted with counting. This would control for aspects of inner speech and mental number representation but lack the extra mathematical cognitive element. The subtraction of the counting part of the task in principle allows the specific cognitive aspect of mathematics to be looked at in isolation. Nevertheless, general processes relating to effort may remain: In PET, the regional increase in brain activity is inferred from task-coupled regional increase radio-labeled blood flow or metabolism. In a review of 107 PET studies, the same region of dorsal anterior cingulate cortex was shown to be activated across a range of different experimental tasks (Paus et al., 1998), suggesting that the region was involved nonspecifically in behavioral or cognitive effort (arising from the extra elements in the active versus control task). Similar observations were made in relation to deactivation of ventromedial prefrontal, subgenual and posterior cingulate cortices when people engage in demanding tasks (Raichle et al., 2001), leading to the proposal of "default mode" or resting network. These observations link performance of effortful, attentionally demanding tasks to the predictable activation and deactivation of regions of cingulate cortex. By extension, these studies suggested that the changes in autonomic bodily state that accompany and presumably facilitate effortful behavior and cognitive performance are linked to the same neural processes.

The simultaneous measurement of an autonomic parameter during functional brain imaging of cognitive processing provides a means of dissecting neural substrates, supporting cognition along different psychophysiological dimensions (examples given in Fig. 6.1). Studies have been undertaken, testing for brain correlates of experimentally provoked changes in autonomic physiology including heart rate (King et al., 1999; Wager et al., 2009a, b), sympathetic skin response (Fredrikson et al., 1998; Critchley et al., 2000b; Patterson et al., 2002), blood pressure (e.g., Critchley et al., 2000a; Harper et al., 2000; Gianaros et al., 2005) and baroreflex suppression (e.g., Gianaros et al., 2012). Following the

Autonomic axes used in psychophysiology studies

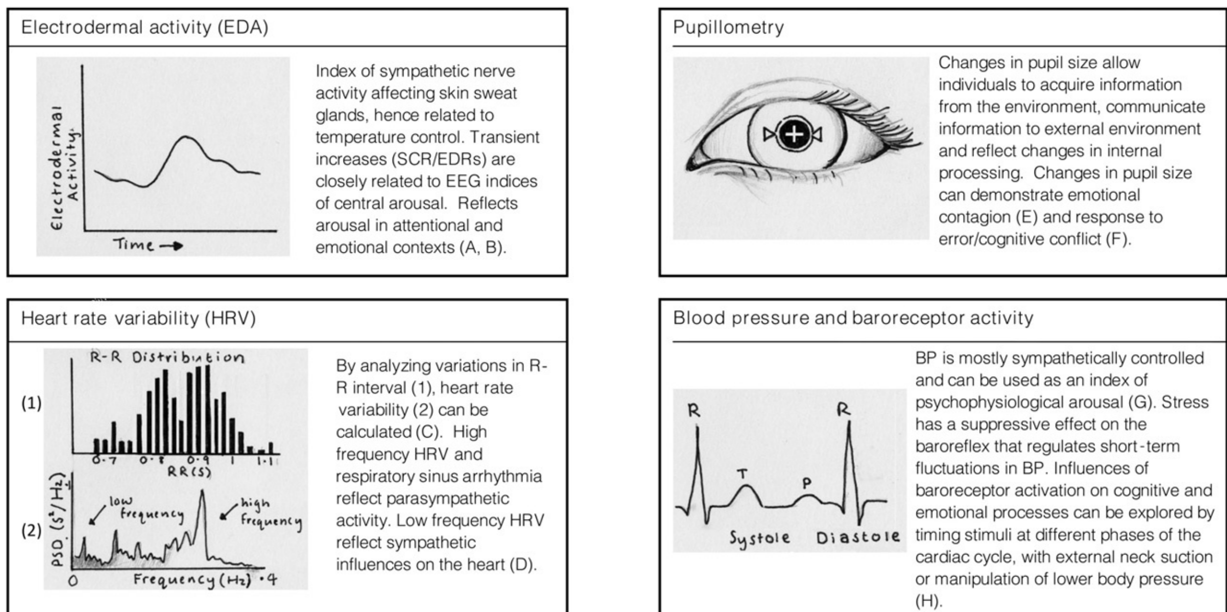

Fig. 6.1. This figure illustrates the role of psychophysiology in investigating integration of autonomic nervous system with cognition and emotion. The above measures provide axes of autonomic activity that can be monitored during neuroimaging and laboratory tasks, allowing integrative analyses. (A) SCL negatively correlates with vmPFC activity. (B) SSR positively correlates with dACC and insula activity (Nagai et al., 2004b). (C) High-frequency HRV correlates with PAG and left insula activity. (D) Low-frequency HRV relates to changes in dACC and bilateral insula. Reduced high frequency HRV may relate to endophenotypic marker of vulnerability to affective disorder (Gray et al., 2009). (E) Observing pupil changes in another activitates Edinger–Westphal nucleus in observer (Harrison et al., 2006); discordance between observer and observed papillary changes activates bilateral insula, left amygdala and ACC (Harrison et al., 2009). (F) Stroop errors increase pupil changes, correlated with activity in dACC and dMPF (Critchley et al., 2005c). (G) Increased dCC reflects increased blood pressure after stress (mental or physical exercise) (Critchley et al., 2000a). (H) Using fMRI, stimuli presented before and during systole elicited differential changes in amygdala, anterior insula and pons activity, engendering different effects on BP (Gray et al., 2009).

observation of anterior cingulate changes described (Paus et al., 1998), the integration of autonomic changes with task engagement was explicitly explored in a set of PET and fMRI studies. When healthy participants performed easy and difficult versions of mental arithmetic (serial subtractions) and a motor exercise (isometric handgrip) tasks during PET scanning, dorsal cingulate activity was enhanced and importantly this activation correlated with task increases in blood pressure (Critchley et al., 2000a). These findings were replicated initially in healthy older subjects and found to be perturbed in patients who lacked peripheral autonomic response (Critchley et al., 2001c). An adapted version of this task was also undertaken in fMRI with simultaneous electrocardiography (ECG): frequency components of heart rate variability were measured during isometric exercise and high- and low-demand working memory tasks (Critchley et al., 2003). Measures of heart rate variability power at high and low frequency bands were derived using rectified band-pass filtering and regressed against measured changes in regional brain activity, controlling for the stimulation and movement parameters of the experimental task. The low frequency component, encompassing sympathetic neural influences on heart rate variability, positively correlated with changes in neural activity within dorsal cingulate (mid, extending anteriorly toward the callosal genu) and bilateral insula cortex (along with regions of thalamus and dorsal brainstem). This observation also complemented findings implicating anterior cingulate in behaviorally integrated sympathetic drive. Correspondingly, abnormalities in sympathetic cardiovascular response were observed in patients with dorsal cingulate lesions (Critchley et al., 2003).

Studies have also targeted electrodermal activity as an autonomic index of orientation, task engagement, cognitive possessing or stimulus potency (Fredrikson et al., 1998; Critchley et al., 2000b; Williams et al., 2000; Patterson et al., 2002). As with cardiac studies, activity within medial frontal and cingulate cortices

typically correlates with sympathetic neural changes in the skin, but there appears to be more variability, suggesting characteristics of the experimental task (perceptual, cognitive, motivational) influence more this relationship between cortical and electrodermal autonomic activity (Critchley, 2009). One autonomic biofeedback study required participants to volitionally increase and decrease skin conductance during neuroimaging and examined the brain correlates of short-term phasic fluctuations in sympathetic activity (corresponding to sympathetic skin responses, SSRs) as distinct from tonic drifts in skin conductance level (SCL) (Nagai et al., 2004b). In keeping with earlier observations (e.g., Fredrikson et al., 1998), SSRs were coupled to dorsal cingulate activity increases (alongside insular and subcortical activation), while the SCL measure of sympathetic tone was negatively correlated with a region of ventromedial prefrontal cortex, extending to subgenual cingulate. This study made an explicit link between regions of the proposed "default mode network" and the control of bodily arousal, suggesting close coupling between resting brain activity with antisympathetic effects (Nagai et al., 2004b).

These and related observations led to a heuristic model of the functional topography of medial frontal cortices in relation to the integration of autonomic control with cognition, emotion, and volitional behavior. Supragenual regions of anterior and mid cingulate were linked to efferent sympathetic influences while ventromedial prefrontal and subgenual cingulate cortices were linked to antisympathetic and parasympathetic (Gianaros et al., 2004; Matthews et al., 2004) influences on autonomic bodily state (Critchley, 2004). Recently, findings endorsed the "two channel" heuristic model: using a social stress task to provoke changes in cardiovascular state, increased activity within dorsal/midcingulate and decreased activity within ventromedial prefrontal cortex both independently predicted increases in evoked heart rate (via thalamus and periaqueductal gray matter) (Wager et al., 2009a). In such experiments, neuroimaging (with fMRI) is not typically very sensitive to proximate, brainstem (and hypothalamic) correlates of autonomic control. This is largely for technical reasons but also perhaps because the housekeeping/homeostatic role of medullary autonomic centers is more continuous, showing less step-change in regional neural activity than the dorsal pons and periaqueductal gray matter (Critchley et al., 2001b; Gray et al., 2010a). Medullary centers are hence potentially less "imageable," requiring more specialized, nonstandard imaging approaches.

Autonomic expression of cognitive conflict and error detection

Psychophysiology highlights the link between changes in bodily arousal state and the behavioral significance of stimuli and actions. In the case of threat, a change in bodily arousal is part of a protective response, i.e., an evolutionarily selected, survival-related response repertoire where the evoked shift in bodily state facilitates an adaptive behavior, e.g., escape motor action. The same type of shifts in body state also occur during types of "cold" cognitive processing, for example, when behavioral strategies need to be changed. One view, promoted especially by Damasio and colleagues, is that fluctuations in bodily arousal contribute to cognitive processes themselves, and feed back to influence and bias thoughts, judgments, and behaviors (Damasio et al., 1991a). This may be particularly useful in correcting suboptimal behaviors.

Certain cognitive tasks, such as the Stroop interference task, evoke demands on attentional processes through cognitive conflicts that are measurable behaviorally from response times, autonomic reactions, and behavioral error. In the "standard" color-word Stroop task, a participant reads from a list of words written in different ink colors. The words are all names of colors. The participant then goes through the list again, naming the ink color of the words while ignoring what is actually written. It is harder (i.e., participants are slower and/or make more errors) to name the ink color (e.g., red) of a word for a different color (e.g., blue). Such cognitive conflict (interference) is generated where a response is required that goes against a prepotent or "more natural" response to the stimuli. Stroop task performance is particularly associated with the engagement of dorsal anterior cingulate cortex. One influential formulation attributes cingulate activation to more than attentional demand, suggesting its central role in rapid detection and signaling of cognitive conflict and behavioral error (e.g., Bechtereva et al., 1990; Dehaene et al., 1994; Bush et al., 2000). An imaging study set out to unpick how the role of dorsal anterior cingulate in effort-related autonomic control might relate to cognitive conflict and error detection: The study measured task-evoked changes in brain activity and autonomic response (here sympathetic influences on pupil size) during performance of a "numerical" Stroop task. It was observed that errors in Stroop task performance elicited greatest effects on pupil diameter, always on trials where there was a conflict (Critchley et al., 2005c). Activity within regions of dorsal anterior cingulate and dorsomedial frontal cortex reflected fluctuations in pupil size and the presence of cognitive conflict in the stimuli. One area in particular was engaged when errors were made that evoked specific high-magnitude pupillary arousal responses. Findings from other studies suggest that this type of autonomic response to error occurs when there is conscious awareness of having made the error (Nieuwenhuis et al., 2001; Hajcak et al., 2003). The imaging study therefore provided insight into a brain area (within dorsal anterior cingulate) integrating adaptive

changes in bodily state with conscious self-monitoring. This physiological signal of a cognitive process may represent what Damasio might term a "somatic marker," shifting the physiological context and feeding back to bias cognitive behavior to avoid further mistakes over ensuing trials (see Fig. 6.2).

Autonomic interaction with decision making

Evidence for interaction between the autonomic nervous system and cognitive processes is perhaps most evident in the context of decision making. Damasio's "somatic marker hypothesis" provided an influential model for this: motivationally important (salient) events trigger automatic changes in bodily state. These changes are mainly envisaged as being autonomic and as reflecting prior experience of that event, usually a negative consequence: Bodily responses mark the occurrence of salient stimuli through feedback, i.e., a parallel somatic/visceral representation of that bodily response. Thus, using information provided by brainstem nuclei, somatosensory context, insula cortex, and amygdala, and mediated through medial frontal cortices (lesion data particularly implicate the ventromedial frontal cortex), visceral/autonomic information is integrated with perceptual information to enhance the representation of important stimuli while shaping both the cognitive and behavioral response. In early accounts of the somatic marker hypothesis, emphasis was given to the unconscious influence of the bodily response on behavior. Experimentally, such effects were illustrated using performance on a gambling task as the "behavioral probe."

Neuroimaging studies following on from the work of Damasio's group have examined the brain activity supporting interaction between autonomic responses and motivational decision making; i.e., gambling task performance. For example, one study, using a card game, revealed activity within dorsal anterior cingulate cortex in anticipation of the outcome of risky decisions that reflected both the degree of risk in the gamble and the state of sympathetic electrodermal arousal when anticipating the outcome of the gamble (Critchley et al., 2001a). A similar observation using "wheels of fortune," indicated the importance of agency in the decision-making process: heart rate increased if a participant actively selected which gamble they wanted to play, despite outcomes having the same monetary value. This physiological shift occurred in anticipation of the outcome and in response to the feedback given at outcome. Notably the genual and dorsal anterior cingulate cortex was engaged at outcome, reflecting both the agency and the autonomic state accompanying that agency (Coricelli et al., 2005). These studies highlight the integrative contribution of autonomic response to brain activity during decision making.

The attention drawn by the somatic marker hypothesis to decision making and the influence of autonomic/somatic bodily state coincided with broadening of interest in choice selection in motivational behavior accompanying advances in economic theory. The result is the growth of a discipline now known as neuroeconomics that attempts to understand the basis of rational and irrational choices. Economic theory used to emphasize the notion that optimal decision-making is rational, maximizing gains, minimizing loss with some cost to risk (i.e., Bayesian maximization of expected utility). Such models assume that deciders possess infinite knowledge and information-processing power to inform their decisions (Naqvi et al., 2006). This view also implicitly argues that emotions should either be excluded from the study of rational decision making, or studied as a detrimental influence. Emotional neuroscience and psychophysiological research now challenges the view that rational choice and emotional processing are unrelated or opposed, with evidence for potential beneficial effects of emotion responses on decision making (Bechara and Damasio, 2005). The autonomic nervous system is an important mediator of these effects: autonomic responses reflect learning of the behavioral value of stimuli, and the central feedback of autonomic bodily changes can influence behavioral judgments. Experimentally this influence can be shown to act implicitly or explicitly, to guide behaviors that maximize reward and avoid punishment (Damasio et al., 1991b; Bechara et al., 1997) (Fig. 6.2).

Changes in peripheral physiology prepare the body for behavior modification; thus it follows that brain areas sensitive to peripheral physiological fluctuations may also modify decision making. The ventromedial and orbitofrontal cortices are implicated in the computation of reward and punishment contingencies (Roberts, 2006). The anterior cingulate is activated during a variety of decision-making processes such as conflict resolution (see above and Pochon et al., 2008). Anterior cingulate with the anterior insula is implicated in the production of subjective feeling states arising out of visceral bodily sensations and the coordination of appropriate responses to internal and external events (Medford and Critchley, 2010). In the formulation of the somatic marker hypothesis it was noted that individuals with vmPFC damage are impaired in their ability to modulate behavioral choice in a gambling task following prior losses (Bechara et al., 1997), an effect coupled to attenuated autonomic reactivity. It is worth noting that the bodily response can be specific: during a stochastic learning task, error-related feedback elicited a deceleration in heart rate (correlating with a specific electroencephalogram potential), while feedback indicating success induced a corresponding increase in heart rate (Groen et al., 2007).

Emotions through central and peripheral states can be detrimental to particular types of decisions. Patients with deficits in the expression of emotion can show enhanced, rational decision making, reflecting this removal of emotional bias (Shiv et al., 2005a, b; Di Martino et al., 2009). Changing moods influence the cognitive weighting of decision parameters, with low mood (and implicitly low autonomic reactivity) linked to a preference for low-risk, low-reward outcomes (Smith and Ellsworth, 1985), while anxiety (typically engendering heightened sympathetic tone) leads to a heightened intolerance of uncertainty (Stern et al., 2009). Together these studies illustrate the integration of autonomic control with cognitive processes underlying decision making.

Autonomic effects on memory

Memories are influenced by attention, arousal, and emotion: processes coupled to each other and to autonomic state. Increased central arousal, typically induced by emotional events, enhance memory encoding and facilitate subsequent memory recall (Cahill and McGaugh, 1998). Moreover, memory retention can be predicted by autonomic indicants such as heart rate response and electrodermal activity. Pharmacological agents that enhance peripheral and central sympathetic action can enhance memory (Cahill and McGaugh, 1998); in contrast, β-adrenergic antagonists that attenuate sympathetic activity can impair memory, particularly of emotional material (Cahill and McGaugh, 1998; van Stegeren et al., 1998; Kroes et al., 2010). Interestingly, memories founded upon familiarity (in the absence of recollection) are also marked by increased autonomic activity, as indexed by electrodermal (Morris et al., 2008) or pupillometric (Heaver and Hutton, 2011) change, raising the intriguing possibility that the representation of these bodily changes may mediate the feeling of "knowing" ascribed to such memories (Morris et al., 2008). Correspondingly, subjective memory impairment is a common symptom in people with autonomic failure (Heims et al., 2006).

Sensitivity to autonomically mediated changes in one's body, i.e., "interoceptive awareness," plays a role in mediating the influence of autonomic state on memory (Fig. 6.2). The notion of interoceptive awareness will be

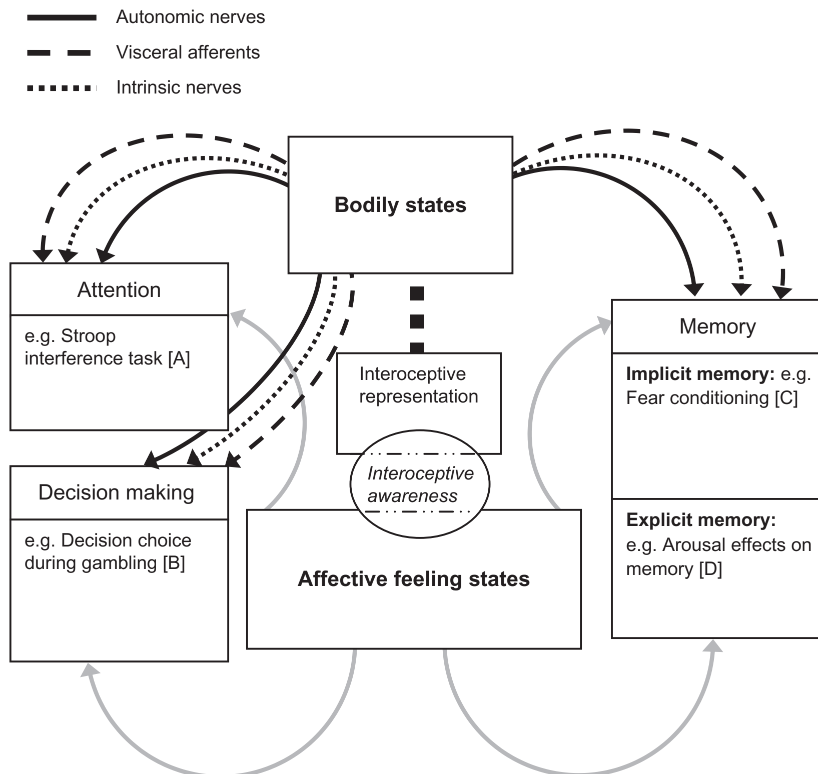

Fig. 6.2. Fluctuations in bodily arousal and affective feeling states can influence cognitive processes. Errors in a stroop interference task are associated with increased pupillary responses ([A] Critchley et al., 2005c). Bodily states and affective feeling states can also guide behaviors, such as decision making during gambling (e.g. [B] (e.g., Bechara et al., 1997; Critchley et al., 2000a)). Emotional events can influence both affective feeling states and increase central arousal, leading to enhanced memory encoding and facilitated memory ([D] Cahill and McGaugh, 1998). Bodily states, synonymous with "gut feelings," can also guide implicit memory processes ([C] Katkin et al., 2001). The propensity for individuals to utilize information conferred in bodily states is mediated by intersubject variability in interoceptive awareness, with some subjects better able to detect fluctuations in bodily processes and thus use the information inherent within those fluctuations to guide cognitions and behaviors (e.g. [C] Katkin et al., 2001).

revisited in this chapter. It is predicated on the concept that some individuals are more influenced by their internal bodily states (of arousal) and as a consequence have better conscious awareness of autonomic processes. Differences in the degree of interoceptive awareness can be tested using behavioral tasks, for example, heartbeat detection, which attempt to measure the accuracy of conscious awareness of individual heartbeats at rest. One version of this task asks the participant to judge if audible notes are in time or delayed relative to individual heart beats (e.g., Whitehead et al., 1977; Wiens et al., 2000); another version asks the participant to count the number of heartbeats occurring over fixed time intervals (Schandry, 1981). Using such approaches participants can be categorized into groups of high and low interoceptive awareness.

Individuals with high interoceptive awareness perform better on specific memory tests, perhaps because the pattern of autonomic change during stimulus processing, or evoked by recollection, can provide additional information to support memory endorsements. In a seminal paper investigating the relationship between interoceptive awareness and memory for emotional information, a fear conditioning paradigm was used in conjunction with the subliminal presentation of emotional stimuli (Katkin et al., 2001). During fear acquisition, snakes and spiders were subliminally presented, and shocks followed one class of stimuli (e.g., snakes; CS+) but not the other (e.g. spiders; CS−). Participants rated the likelihood that these stimuli would be followed by a shock and it was found that interoceptive awareness predicted participants' shock prediction accuracy. The interpretation was that participants with high interoceptive awareness use the perception of visceral cues generated in the nonconscious fear paradigm to facilitate the subsequent recognition of emotional stimuli. Participants with high interoceptive awareness also show enhanced later recognition memory for emotional pictures (Pollatos and Schandry, 2008) and words (Werner et al., 2010). These observations are interesting since they extend a theoretical prediction that those individuals with either greater autonomic response or enhanced access to bodily information have extra cues to facilitate memory retrieval. Thus one way through which autonomic responses influence memory is mediated by interoceptive sensitivity (Katkin et al., 2001) (Fig. 6.2). It is noteworthy the cognitive impact of autonomic arousal states and their central representation is most evident in the processing of emotional information.

AUTONOMIC INTEGRATION WITH EMOTION

Definition and autonomic expression of emotions

There exist different conceptualizations and seemingly contradictory theories of emotion in the literature. A prevalent view sees emotion as a transient perturbation in ongoing behavioral functioning evoked by an external or internal triggering stimulus (defined as emotive by this capacity). A working definition is that emotions are stereotyped response sequences and biases to subsequent behavior, which include these experiential, physiological and behavioral components. Emotions enrich human experience and have communicative social impact; emotive stimuli are assigned heightened value, bias attention and memory, and affect motivational drives and reorient ongoing behavior (Scherer, 2000; Dolan, 2002). Evolution appears to have selected for a set of "basic" emotions, fear, happiness, anger, disgust, surprise, and sadness (Darwin, 1872; Ekman et al., 1969; Ekman and Friesen, 1971), that are universal; they are present across all human cultures.

The obligatory role of physiological response, notably autonomically mediated bodily changes to emotion, is one area of controversy (Harrison et al., 2011). There is some empirical evidence for the coupling of individual basic emotions to discrete patterns of autonomic response, e.g., changes in heart rate, skin conductance, and skin temperature (Levenson, 1992), or distinguishable patterns of cardiorespiratory activity (Rainville et al., 2006). No single autonomic dimension (e.g., sympathetic arousal) appears to be sufficient to characterize different emotions (Rainville et al., 2006). Characteristic (modal) and diverse alterations in physiology with specific basic emotions continue to be mapped out (see Kreibig, 2010, and Harrison et al., 2011, for recent reviews). In sum, there are degrees of emotion-specific patterning that variably overlap across emotion categories.

Stimuli within basic emotion categories elicit differential physiological responses depending upon factors such as psychological state of the viewer (e.g., viewing anger stimuli can elicit a fear response, or lead to the mirroring of an anger response) and motivational direction (e.g., withdrawal-orientated anger can elicit a decrease in heart rate, self-directed anger an increase in heart rate (Stemmler et al., 2007)). Within disgust, class of stimuli can also influence physiological responding: core contamination disgust (e.g., unpalatable food, foul smells, dirty toilets) causes increases in both sympathetic and parasympathetic indices, manifest as increased/unchanged heart rate, increased heart rate variability (HRV), decreased stroke volume, enhanced peripheral resistance, and an increase in respiration rate and effects on the stomach (tachygastria). Body boundary violation disgust (e.g., injections, mutilation scenes, bloody injuries) are characterized by reduced heart rate, increased electrodermal activity, increased respiration rate, unchanged stroke volume, and total peripheral resistance (Harrison et al., 2010).

The heterogeneity of emotion-specific physiological responses found in meta-analytical studies (Cacioppo

et al., 2000) has led to dismissal of any predictive association, e.g., "it is not possible to confidently claim that there are kinds of emotion with unique and invariant autonomic signatures" (Barrett, 2006). Instead, patterns of physiological response are proposed to follow more general dimensions of threat and challenge, and positive versus negative affect with autonomic activity is "mobilized in response to the metabolic demands associated with actual behavior or expected behavior." Since behaviors are neither emotion-specific nor context-invariant (Lang et al., 1990), *a priori* emotion-specific autonomic patterns are therefore rather improbable (Barrett, 2006). A different view asks why autonomic responses would not convey emotion-specific activation patterns, given their specific functions of individual emotions for human adaptation (Stemmler, 2004). Since emotions have distinct goals, they ought to require differentiated autonomic activity for body protection and behavior preparation. Nevertheless, the emphasis is on integrated patterns of response rather than single isolated changes (Hilton, 1975; Stemmler, 2004; Mauss and Robinson, 2009).

Meta-analyses of physiological responding in emotion indicate an intermediate position with context-specific emotional effects of autonomic activity (Cacioppo et al., 2000). Valence-specific (good or bad) patterning is more generally consistent than emotion-specific patterning. However, it has been argued that the greater autonomic responses to negative emotions may be an artifactual consequence of the tendency to compare one positive emotion (happiness) with many more negative emotions (e.g., fear, sadness, anger, disgust) (Kreibig, 2010). Inclusion of multiple positive emotions (affection, amusement, contentment, happiness, joy, pleasure, pride, and surprise) can improve the observed degree of emotion-specific physiological patterning (Kreibig, 2010).

Central generators of emotional autonomic change

Anterior cingulate activity is associated with generation of sympathetic autonomic responses in the context of emotional processing; again there appears to be some relation to the nature of the task and with the precise autonomic response measured. The effects of emotional processing on cardiac responses have been studied using forewarned reaction time tasks: such tasks induce predictable changes in both brain activity and autonomic bodily responses. A warning stimulus (cue) signals that the participant should respond to the next imperative stimulus with a reaction time response. In the period between cue and imperative stimuli, there is an orienting response to the cue stimulus followed by cardiac deceleration prior to the imperative stimulus and response. An electrocortical potential (the contingent negative variation, CNV) also occurs during this anticipatory interval, indicative of thalamocortical excitability and ascribable in part to dorsal cingulate activation (e.g., Nagai et al., 2004a). An emotional version of the forewarned reaction time task replaced the imperative stimuli with faces depicting different emotional expressions. The reaction time response was a choice judgment of the emotion portrayed. By measuring cardiac responses to the face stimuli it was possible to examine brain activity associated with differential cardiac responses (orienting acceleration and deceleration) to different emotional expressions. In fact the accelerative and decelerative cardiac responses were closely correlated. Processing of happy and disgust faces attenuated, while processing sad and angry faces enhanced heart rate responses. Brain activity reflecting emotional effects on heart rate within and between the different categories of emotional processing was enhanced in regions including anterior cingulate cortex, amygdala, and temporal lobe (lingual and fusiform) cortices (Critchley et al., 2005a). Similar brain areas are activated in sexual arousal, reflecting activity in autonomic, cognitive, and emotional areas, including hypothalamus activity and claustrum (Georgiadis et al., 2009; Kuhn and Gallinat, 2011).

The emotional effects observed on heart rate were consistent with those observed in other contexts, notably Ekman and coworkers' studies on differential autonomic responses to emotion (Ekman et al., 1983). The basic principle, greater parasympathetic and perhaps less sympathetic activation associated with happiness and disgust and a shift toward sympathetic dominance and parasympathetic activity with sadness and anger, is replicated in other contexts and to other stimulus sets (e.g., Umeda et al., unpublished observations). These studies highlight a degree of emotion-specificity of autonomic response that is nevertheless crude compared to the organ-specific control visible as changes in posture and skin perfusion that characterize the expression of different emotions for which autonomic patterning is the rule.

The central nucleus of the amygdala is implicated as a generator of emotional autonomic activity, particularly in the context of fear processing. The amygdala is involved in learning fear, such that patients with temporal lobe lesions affecting the amygdala demonstrate impaired fear conditioning through absent autonomic (electrodermal) reactivity to threat (LaBar et al., 1995). In fact, the degree to which healthy people activate amygdala when learning about threat correlates with the degree of autonomic response to the threat (LaBar et al., 1998). The role of the amygdala in signaling behaviorally and autonomically the salience of emotive stimuli has led to its inclusion, alongside anterior cingulate and insula cortex, within the "salience" network (Menon and

Uddin, 2010). However, it is worth noting that neuroimaging studies using emotional paradigms are variable in the extent to which autonomic responses are found to correlate with amygdala activity (e.g., Wager et al., 2009a). Moreover, there is evidence to link the amygdala also to afferent representation of internal physiological state (Harrison et al., 2009).

Autonomic contributions to emotional feeling states

Historically, theories of emotion have given different weights to the necessity of autonomic responses for emotional feeling states. Peripheral theories of emotion argue that the origins of emotional feelings stem from bodily responses. Based on this premise, the seminal James and Lange theory of emotion argued that emotions depend entirely on (feedback from) the bodily response:

> *We owe all the emotional side of our mental life, our joys and sorrows, our happy and unhappy hours to our vasomotor system. If the impressions which fall upon our senses did not possess the power of stimulating it, we would wander through life unsympathetic and passionless, all impressions of the outer word would only enrich our experience, increase our knowledge, but would arouse neither joy nor anger, would give us neither care nor fear.*
>
> *(Lange and James, 1967)*

However, Cannon argued that bodily arousal responses are too undifferentiated to account for the variety of distinct emotional feeling states (Cannon, 1927). Subsequent attempts have been made to reconcile these distinct views by incorporating the role of cognitive appraisal. The two-stage model of Schachter and Singer argued changes in peripheral arousal can elicit subjective emotionality "of corresponding intensities," yet, the nature of the emotion category is determined by cognitive context (Schachter and Singer, 1962). Thus, emotional states are states of arousal, whose type (e.g., fear, happiness, sadness) is determined by the cognitive interpretation of what evoked that state. The somatic marker hypothesis, discussed above (Autonomic interaction with decision making), conceptualizes emotions and emotional feeling states along similar lines, with perhaps a more negative bias.

Studies in clinical populations with altered peripheral physiological responses and altered affect provide insight into the relationship between autonomic patterning and subjective emotional feeling states. It is recognized that emotion behaviors (e.g., pathological laughter) can deviate from peripheral physiological state but such instances are the exception (Parvizi et al., 2001). The absence of peripheral autonomic response, for example, in patients with pure autonomic failure (PAF), an acquired failure of peripheral autonomic regulation, may lead to subtle blunting of emotional feeling (appearing less anxious relative to comparably debilitated Parkinson's patients without autonomic failure (Mathias, 2003; Critchley, unpublished observations)), but these effects are subtle relative to other emotional changes (see below). The uncoupling of brain and body that occurs in part following high spinal cord transection has been suggested to lead to altered emotions. However, while changes in brain response to emotive stimuli are demonstrable (Nicotra et al., 2006), there is little evidence for attenuation of emotional feelings in patients with high spinal cord transaction or for change in emotion reactivity that cannot be explained by adjustment to disability or chronic pain (Deady et al., 2010).

Interoceptive sensitivity and insula cortex

Interoceptive awareness is mentioned above (Autonomic effects on memory) and much of the motivation for defining individual differences in interoceptive sensitivity comes from peripheral theories of emotion, where the prediction is that people more attuned to (autonomic) bodily responses experience emotions with heightened intensity. As noted, the emphasis has been on heartbeat detection, both because heartbeats are distinct internal events that can be easily measured and because people's ability to detect heartbeats correlates with their ability to detect changes in other autonomically innervated organs (Whitehead and Drescher, 1980). Cranial nerves (mainly vagus) and spinal cord pathways (particularly the lamina I spinothalamocortical pathway) (Craig, 2002) proved the major routes of visceral functional and autonomic feedback to the brain. Insula cortex appears to be particularly important in the cortical representation of internal state, with right anterior insula subserving interoceptive awareness and its expression as emotional feeling states (see below) (Critchley et al., 2004) and the interaction of interoceptive information with the conscious appraisal of other information (Critchley, 2004; Singer et al., 2009).

A neuroimaging study used a heartbeat detection task to reveal engagement of insula, anterior cingulate and somatosensory cortices when people focus on their internal bodily processes. Awareness and sensitivity to the occurrence of individual heartbeats was revealed by how well people distinguished the presence of a heartnote delay in auditory tones triggered by individual heartbeats. Across participants, activity and even gray matter volume within one brain region, right anterior insular cortex, predicted differences in interoceptive

sensitivity (Critchley et al., 2004). The link with emotional process was revealed by showing that interoceptive sensitivity and activity/volume within right insula cortex also reflected day-to-day experiences of anxiety (and to a lesser extent other negative emotions). This study reinforced proposals put forward by Craig that right anterior insula cortex in primates is the terminus of afferent viscerosensory information. Since information mapped by this system was essentially of motivational significance, Craig proposed that insula cortex represents motivational state and through rerepresentations becomes the substrate for conscious feeling states (Craig, 2002, 2003).

The role of insula cortex in the integrative representation of emotional feeling states that originate in bodily responses was particularly highlighted by a study of disgust: combining electrocardiography, electrogastrography, and functional magnetic resonance imaging, the distinct physiological effects of core (nauseating) disgust and body boundary violation disgust (evoked by video sequences) were mapped into activity within discrete subregions of insula cortex that predicted the magnitude of subjective disgust reported by the observer (Harrison et al., 2010). This study suggested again the origin of emotional feelings in the cortical representation of bodily states.

Perturbation of visceral afferent information: relationship to neural correlates and affect

Visceral stimulation modulates activity within brain areas implicated in affective processing. Investigating changes in internal bodily state via direct gastrointestinal stimulation of esophagus or large bowel reveals enhanced activity within cingulate and insula cortex. This occurs even in the absence of pain, though potentially still reflects affective processing of rectal sensation (Hobday et al., 2001). Anorectal stimulation provides segregation of somatosensory (anal) versus visceral (rectal) afferents within the nervous system (Eickhoff et al., 2006). Bilateral insula and dorsal anterior cingulate cortex are activated by rectal (but not anal) stimulation, reflecting heightened propensity for visceral sensations to be displayed in those areas involved in affective processing (Hobday et al., 2001). The ventromedial prefrontal cortex is another key area; observations in patients with spinal cord lesions and from a single patient treated with vagus nerve stimulation for depression highlight its role in the integration of afferent visceral sensory information perturbed by interference with spinal and vagus nerve routes (Nicotra et al., 2006; Critchley et al., 2007). Surprisingly, there does not seem to be an obvious functional hierarchy in these effects, something that other data also suggest. The conclusion here is that anterior insula, dorsal anterior cingulate, and ventromedial prefrontal cortex contribute to the integration of visceral afferent information, generated by salient stimuli with stimulus processing itself.

Beat-to-beat effects: relationship to neural correlates and affect

General perturbations in interoceptive state modulate activity within similar brain areas to those resulting from visceral stimulation (i.e., areas involved in affective processing). Afferent information from the viscera influences stimulus processing even at the level of individual heartbeats (Lacey and Lacey, 1978, 1980). At systole the pressure wave of cardiac ejection activates aortic and carotid baroreceptors. Baroreceptor effects influence the processing of painful and strong unexpected somatosensory stimuli to modify cortical reflexive and autonomic response (Donadio et al., 2002; Edwards et al., 2003; Wallin, 2007). Efferent sympathetic responses to stimuli occurring at systole are modulated and notably there is inhibition of muscle sympathetic nerve traffic while sympathetic electrodermal responses are unaltered. These effects are amplified in patients with blood phobia and syncope, suggesting that these mechanisms are central to traits in emotional behavior and reactivity (Donadio et al., 2007). The phasic signature of this channel, reflecting short-term fluctuations in visceral state within each cardiac cycle, can be exploited in the study of autonomic interactions with emotion to reveal corresponding neuronal correlates. Our own neuroimaging observations (Gray et al., 2010b) reveal that the interaction between stimuli and baroreceptor activation within the cardiac cycle is mediated by differential engagement of a discreet set of brainstem, cortical, and subcortical centers to elicit further characteristic changes in autonomic state. Significantly, these effects can influence processing of emotional stimuli (Gray et al., 2012). Gray et al. (2012) investigated the interaction between emotional appraisal and cardiovascular activity by presenting emotional stimuli at distinct points within the cardiac cycle. Combining a forewarned reaction time task with discrete emotional facial expressions, face stimuli were presented at either the end of diastole (indexed by the ECG R-wave) or systole (approximately at the ECG T-wave) when baroreceptor impulses are processed centrally. Using a behavioral index of emotional intensity, ratings of disgust increased when stimuli were processed at systole. This was in contrast to other emotions (happiness, anger, sadness), where intensity ratings were not modified by cardiac cycle. PAG appeared to

underlie the moderating effect of cardiac timing on emotional appraisal, whereby the negative association between PAG activity and subjective intensity was significantly enhanced when emotional stimulus presentation was synchronous with R-wave relative to T-wave. Rebound heart rate responses were attenuated following disgust and happy stimuli, replicating prior research (Critchley et al., 2005a), and localized orbital frontal activity predicted heart rate response to emotional stimuli. This finding is in line with the integrative role of orbitofrontal cortex in combining "cognitive and perceptual cross-modal representations with motivationally-salient physiological information and is a cortical source of descending influences on internal bodily state" (Gray et al., 2012).

Autonomic communication and empathy

The neural integration of cognitive, affective and autonomic response is proposed to be a guide to adaptive social behavior (Damasio et al., 1991a; Damasio, 1994, 1999). The mirroring of changes in visceral state during emotion may be mirrored in the responses of others, permitting a corresponding representation in the observer. The degree to which individuals are susceptible to this "contagion" predicts individual differences in questionnaire ratings of empathy. The notion that affective feelings are coupled to autonomically mediated visceral responses implies that the sharing of emotional feelings empathetically embodies a sharing of visceral autonomic response across individuals. A dependence of emotional interchange on aspects of autonomic reactivity is suggested from observations in patients with PAF, who manifest a blunting of empathetic responses on a questionnaire measure of emotional empathy (Chauhan et al., 2008). With many autonomic responses serving as visual signals of emotion, reciprocation is visibly evident in the contagion of fear (including facial pallor) and anger responses (facial flushing), but in many cases the exchange is subtle and the signals are covert.

Pupillary signals influence emotional processing (Harrison et al., 2006, 2007). Student volunteers were asked in a behavioral task to make visual analog ratings of positive/negative, intensity and attractiveness attributes of pictures of emotional faces. For each identity/expression combination, the size of the stimuli pupils was digitally manipulated to cover a range of (biologically plausible) sizes. Participants were not informed of this image manipulation and none were aware of this at debriefing after the task was performed. Contrary to the initial prediction that enlarged pupils, reflecting sympathetic activity, would produce greater intensity ratings of all the emotions, no significant (linear) effect of pupil size was observed for any of the emotions except sadness. Here the smaller the pupils the more negative and more emotionally intense sad faces were rated. Interestingly, the degree to which participants were affected by this covert manipulation of perceived pupil size correlated with individual differences in questionnaire measures of emotional empathy. A parallel neuroimaging study was conducted with the same pupil-manipulated face stimuli. Participants made age judgments of the faces, processing both emotion and the manipulated pupil size incidentally. During scanning with fMRI, it was also possible to use pupillometry to record the pupillary response of the participant to the stimuli. Activity changes in amygdala, insula, superior temporal sulcus, and brainstem (in the region of the Edinger–Westphal nucleus) reflected the interaction between perceived pupil size and sad versus non-sad emotion. When the pupil responses of the participants were examined, it was found that there was coherence in the observed and observer's pupils only in the context of sadness (i.e., seeing a sad face with small pupils caused the participants' own pupils to constrict more). The extent to which this occurred was again predicted by activity within the Edinger–Westphal nucleus (the autonomic nucleus responsible for pupillary control).

These observations show a contagion of autonomic responses in emotional processing, highlighting automatic mirroring only in the context of sadness perception that influences the judgment of sadness in a manner related to individual differences in empathy for others. Moreover, the findings highlight the presence of organ specificity in emotional autonomic responses that are integrated with cognitive and emotional aspects of empathy within a discrete neural system.

"Contagion" of emotion can occur when changes in visceral state during emotion may be mirrored in an observer, inducing a corresponding representation (Critchley, 2009). It thus follows that those individuals with enhanced sensitivity to visceral perception and monitoring have a consequent increased sensitivity to empathetic feeling. Indeed, empirical research has linked enhanced proficiency for interoceptive awareness with a greater capacity for empathy (Fukushima et al., 2011). The amplitude of heartbeat-evoked potentials (HEPs, for affective vs. physical judgments), thought to reflect cortical representation of cardiac signal, correlated with self-rated empathy scores (Fukushima et al., 2011).

INTEGRATIVE MECHANISMS OF STRESS AND RELEVANCE TO HEALTH

Cardiovascular risk

Cardiac risk is enhanced by psychological conditions, including grief and depression, and is associated with

differences in personality and socioeconomic circumstances. Low vagus parasympathetic tone and exaggerated evoked sympathetic (blood pressure and heart rate) response represent putative physiological mediators of cardiac risk (e.g., Carroll et al., 2001; Thayer and Lane, 2007). Studies of at-risk recently bereaved individuals highlight abnormalities in regions, including subgenual cingulate, implicated in parasympathetic influences on the heart that correspond to withdrawal of this cardioprotective "break" (O'Connor et al., 2007). Abnormalities within similar regions of subgenual cingulate and ventromedial prefrontal cortex are commonly reported in depressed patients (who also show diminished parasympathetic tone) (O'Connor et al., 2007). Interestingly, the structural morphology of these and related brain regions in healthy individuals relate to social predictors of cardiac risk, including perceived life stress and social standing (Gianaros et al., 2007a, b). Exaggerated cardiovascular responses to stress also represent a psychophysiological predictor of cardiac morbidity and mortality: across individuals, the response within posterior cingulate cortex predicts individual differences in cardiovascular responsivity, hence, by inference, cardiac risk (Gianaros et al., 2004, 2005). Salient environmental stimuli may motivate alterations in cardiovascular function, over and above physiological motivators such as physical stress, exercise, faint, or hemorrhage. The range of these specific environmental (or experimental) situations that can impact on cardiovascular state is extremely large, reflecting both primary and learned challenges that ultimately evoke mental and physiological stress. Associations are apparent at the population level between environmental stressors and adverse cardiac outcomes such as acute coronary syndromes or sudden cardiac death. For example, the major earthquakes in Los Angeles (Leor et al., 1996) and the Kobe region of Japan (Suzuki et al., 1995) were both followed by significantly increased hospital admissions for acute myocardial infarction (Bhattacharyya and Steptoe, 2007). Similar research suggests that war, terrorist acts, industrial disasters, and even sporting events are associated with higher rates of infarction, disruption of normal cardiac rhythm, and sudden cardiac death. More predictably, increased hospitalization of cardiac patients is observed during Christmas (Reedman et al., 2008), New Year's Eve (Kloner et al., 1999; Phillips et al., 2004), and on Mondays (Barnett and Dobson, 2005), further highlighting associations between times of potential psychosocial stress and cardiovascular dysfunction. Specific emotional states are particularly associated with increased risk of clinically significant cardiac events (Bhattacharyya and Steptoe, 2007). Acute episodes of anger (Mittleman et al., 1995, 1997; Strike et al., 2006), stress (Moller et al., 2005; Vlastelica, 2008), or depression (Steptoe et al., 2006) are significantly over-reported in cardiac patients prior to admission, suggesting negative emotions may trigger adverse cardiac events. Likewise, longer-term exposure to stress may also increase cardiac risk (Willich et al., 1993; Deljanin et al., 2007; Bhattacharyya et al., 2010).

Brain imaging of autonomic risk factors

Blood pressure reactivity during emotional or cognitive stress is a recognized indicator of risk for hypertension, ventricular hypertrophy, and premature atherosclerosis (Krantz and Manuck, 1984; Treiber et al., 2003). Functional brain imaging studies also frequently identify amygdala activity during tasks which induce alterations in cardiovascular function. During incongruent conditions of a Stroop color-word interference task, mean arterial pressure alterations were positively associated with change in bilateral amygdala activity, and volumetric analysis of participants' structural MRI scans revealed gray matter volume within the amygdala negatively correlated with blood pressure reactivity. This same pattern was also observed within genual anterior cingulate cortex and pontine nuclei (Gianaros et al., 2008). Carotid artery intimal media thickness (IMT), measured with ultrasonography, is an indicator of atherosclerosis and a risk factor for a range of cardiovascular diseases including angina, myocardial infarction, and stroke (Lorenz et al., 2007). IMT positively correlates with activity in anterior cingulate cortex and dorsal amygdala during a facial expression matching task (Gianaros et al., 2009). These results add further support for the notion of a cortical network including the amygdala, (insula) and anterior cingulate cortex through which cognitive emotional stressors are translated into changes in cardiovascular function. Moreover, they suggest a pattern whereby exaggerated amygdala responses to emotional stressors are linked to cardiovascular damage as a direct consequence of excessive reactivity to stress (Gianaros et al., 2009).

Arrhythmogenesis

Brain responses to emotional challenges may trigger potentially fatal arrhythmic cardiac events. The presence of pre-existing heart disease greatly increases this risk. Lateralization of efferent autonomic drive from the brain may also be a mediating factor (Lane and Schwartz, 1987): hemispheric dominance of brain responses to powerful emotional challenges may engender a lateralization of sympathetic outflow to the heart, affecting myocardial repolarization. If the electrical initiation of contraction reaches regions of heart muscle before they are fully repolarized, the sequential

coordination of contraction is disrupted, a process already destabilized in cardiac disease. Proarrhythmic changes in myocardial repolarization can be quantified from the morphology of electrocardiographic T-waves across chest leads. Mental stress shifts the heart toward proarrhythmic state, even in healthy people (Taggart et al., 2005). In a PET brain imaging study of cardiac patients, the lateralization of brain responses during stress was tested to identify regions predictive of proarrhythmic changes (Critchley et al., 2005b). Interestingly, right-sided midbrain activity (in the region of the parabrachial nucleus) predicted proarrhythmic cardiac changes and which of the patients were at greatest risk of arrhythmia. A further study using electroencephalography suggests this may be a consequence, in patients with pre-existing heart disease, of lateral dominance of a cardiocerebrocardiac loop governing cardiac contractility (Gray et al., 2007b).

INTEGRATION IN SELF-REPRESENTATION

The concepts

There is a longstanding notion that the mental representation of self is ultimately grounded on the representation of the body, and the consistency of the representation of the internal body ultimately provides the primary reference for the limbs and special senses as the body interacts with the environment. Homeostatic maintenance of the *milieu intérieur* is highly dynamic and controlled through interacting and competing mechanisms. While there is a tendency to see the arrangement of these mechanisms as hierarchical, with conscious experience and volitional behavior somewhere near the top and emotions more proximate to the basic workings of the body-machine, this model is at best heuristic. The concept of allostasis touches on this instability, recognizing that there is inherently no internal stability and that it is more, perhaps, the adaptive process of control of internal state that can be viewed as a consistent factor and the basis for self-reference in its broad sense. Here, by adaptive control, we refer to the integration of the autonomic or behavioral adjustments to change internal states with the afferent feedback signaling the direction of change in internal state and motivating further adjustment. Within the brain, this integration is achieved through prediction errors and efference copies.

Taking as a model the notion that the psychological representation of self is grounded on the control of internal bodily state, there are a number of predictions. First, that the notion of agency is important. Uncoupling autonomic efferent control from the visceral feedback might, if transient, provoke a sense of unease that would require behavioral or psychological adjustment, yet which if persistent might destabilize cognitive and emotional processes established over the life course that are grounded on intact self-representation. Second, processes related to control and representation of internal bodily state will determine the strength of self-representation.

Uncoupling of internal control in clinical groups

Patients with acquired (typically traumatic) high spinal cord transection experience a major uncoupling of their internal and external bodily control. In patients with pure autonomic failure there is a gradual compromise in autonomic effector function. Yet in neither patient group is there any compelling evidence that self-representation is compromised. Clearly, following spinal cord transection, individuals need to adjust psychologically to paralysis and loss of independence with even basic functions. They are vulnerable to depression and chronic pain. Nevertheless, spinal cord transection appears not to limit the range of emotions an individual can experience nor, in itself, compromise emotional responsivity. Psychological adjustment reactions, depression, pain, and loss of physical function often enhance self-reference and bolster subjective sense of self. Similar observations can be made of patients with pure autonomic failure whose apparent pragmatism is often quite noteworthy and in whom it is difficult to identify emotional deficits.

Signatures of self-disturbance

Mismatch and misattribution of interoceptive cues appears key in disorders of the self. In a "comparator model" of schizophrenia, it is proposed that disturbances of self (e.g., delusions of control) arise as a consequence of problems in predictive coding, reflecting confusion between evaluation of changes in sensations caused by the self and changes associated with external causes: Sensory effects of self are attributed instead to external forces (Frith, 2012). A similar prediction error is implicated as a central mechanism in generation of anxiety (a core symptom of many affective disorders including obsessive compulsive disorder and autistic spectrum conditions), with heightened anxiety a consequence of augmented detection of difference between observed and expected bodily states. Insula cortex is proposed to mediate anxiety via (mis)match of interoceptive signals; subjective anxiety is associated with enhanced interoceptive prediction error signals (Paulus and Stein, 2006). Highly anxious individuals show increased anterior insula cortex activity during emotion processing. Inducing mismatch between predicted and actual interoceptive signals via false physiological feedback further demonstrates role of insula cortex (Gray et al., 2007a). Depersonalization and derealization disorders, where the concept of self is also disturbed, show

similar mismatch of interoceptive cues, pain signals may be dulled and their origin misattributed. For example, in an earlier account of the disorder, a patient of Mayer-Gross (1935) reported "I feel pains in my chest, but they seem to belong to someone else, not to me" (p. 114). Patients with depersonalization disorder and schizophrenia show corresponding autonomic disturbances. Depersonalization is associated with blunted autonomic responses, e.g., skin conductance abnormalities (Lader, 1975; Griffin et al., 1997). In bipolar disorder, negative correlations are reported between level of dissociation and autonomic parameters (Latalova et al., 2010). Low heart rate variability and decreased baroreflex sensitivity is found in schizophrenia (Koponen et al., 2008). Interestingly, a signal mismatch is suspected: Kring and Moran report that subjects with schizophrenia exhibit greater skin conductance reactivity in response to emotionally evocative film clips, despite displaying few observable facial expressions (Kring and Moran, 2008). This paradox of increased emotionality (autonomic reactivity and subjective arousal) in the face of deficits in perception and expression of emotion has been attributed to specific intra-amygdala abnormalities (Aleman and Kahn, 2005).

Susceptibility to the "rubber hand illusion," in which synchronous tactile and visual stimulation may lead individuals to experience a false hand as their own, is a useful experimental probe into mechanisms of self-representation and coherence within concepts of agency. Those with disordered self-representation (e.g., schizophrenia patients) are more prone to the illusion (Peled et al., 2000). This can be equally induced by dissociative agents such as ketamine (Morgan et al., 2011) and enhanced by administration of dexamphetamine (Albrecht et al., 2011), which results in elevated dopamine, a mediator of salience in psychosis (Kapur, 2003). Interestingly, a recent study by Tsakaris and colleagues finds that more interoceptively aware individuals are less likely to perceive the rubber hand as their own (Tsakiris et al., 2011). This raises important questions of insight (and its modulation) in disordered self-representation and is a target for further integrated research.

CONCLUSIONS: A FUNCTIONALLY INTEGRATED SYSTEM

We have outlined the motivational integration of cognitive emotional and cardiovascular function, providing examples from recent neuroimaging research which highlight neural systems important in mediating these relationships. At a general level, this research provides insight into brain–body interactions promoting broader understandings of health and disease, consistent with known risk factors for adverse cardiac events including depression, anxiety, and psychosocial triggers. More specifically, we have endeavored to highlight the importance of cortical activity in cognitive emotional and cardiovascular integration. Anterior cingulate cortical activity is recurrently observed during cognitive and emotional experimental paradigms, and also has a demonstrated role in cardiovascular regulation accompanying cognitive and emotional processing, consistent with a role as "visceromotor" cortex. Likewise, insula cortex activity is important in both the regulation and representation of cardiovascular function and may be conceptualized as a "viscerosensory" cortical region (see Craig, 2005). Activity here may assist the integration of visceral and emotional processing, facilitating the coloring of emotional experience by concomitant cardiovascular and visceral activity. Further, the amygdala demonstrates a functional correspondence with stress and emotion effects in the heart and vasculature in addition to its demonstrated contributions to processing emotional and salient stimuli. Activity within these regions may regulate hypothalamic, pons and medullary circuits responsible for coordinated sympathetic regulation of the heart. Recent methodological advances in neuroimaging (i.e., moderation analysis) allow for the construction of statistical models which directly assess the degree to which neural change during stressor tasks mediate cardiovascular changes also accompanying stressor tasks (Wager et al., 2009a). The continuing development of functional neuroimaging techniques that allow the simultaneous investigation of neural and psychophysiological activity *in vivo* (Gray et al., 2009) promise further advances in delineating the integration of cardiac function with cognitive and emotional processing.

REFERENCES

Albrecht MA, Martin-Iverson MT, Price G et al. (2011). Dexamphetamine effects on separate constructs in the rubber hand illusion test. Psychopharmacology (Berl) 217: 39–50.
Aleman A, Kahn RS (2005). Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? Prog Neurobiol 77: 283–298.
Barnett AG, Dobson AJ (2005). Excess in cardiovascular events on Mondays: a meta-analysis and prospective study. J Epidemiol Community Health 59: 109–114.
Barrett LF (2006). Are emotions natural kinds? Perspect Psychol Sci 1: 28.
Bechara A, Damasio AR (2005). The somatic marker hypothesis: a neural theory of economic decision. Games Econ Behav 52: 336–372.
Bechara A, Damasio H, Tranel D et al. (1997). Deciding advantageously before knowing the advantageous strategy. Science 275: 1293–1295.
Bechtereva NP, Kropotov JD, Ponomarev VA et al. (1990). In search of cerebral error detectors. Int J Psychophysiol 8: 261–273.
Bhattacharyya MR, Steptoe A (2007). Emotional triggers of acute coronary syndromes: strength of evidence biological

processes and clinical implications. Prog Cardiovasc Dis 49: 353–365.

Bhattacharyya MR, Perkins-Porras L, Wikman A et al. (2010). The long-term effects of acute triggers of acute coronary syndromes on adaptation and quality of life. Int J Cardiol 138: 246–252.

Bouton ME (1993). Context time and memory retrieval in the interference paradigms of Pavlovian learning. Psychol Bull 114: 80–99.

Bouton ME, Mineka S, Barlow DH (2001). A modern learning theory perspective on the etiology of panic disorder. Psychol Rev 108: 4–32.

Bush G, Luu P, Posner MI (2000). Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4: 215–222.

Cacioppo JT, Berntson GG, Larsen JT et al. (2000). The psychophysiology of emotion. In: MJ Lewis, JM Haviland-Jones (Eds.), Handbook of Emotions, 2nd edn. Guilford Press New York.

Cahill L, McGaugh JL (1998). Mechanisms of emotional arousal and lasting declarative memory. Trends Neurosci 21: 294–299.

Cannon WB (1927). Bodily changes in pain hunger fear and rage : an account of recent researches into the function of emotional excitement. D Appleton, New York.

Carroll D, Smith GD, Shipley MJ et al. (2001). Blood pressure reactions to acute psychological stress and future blood pressure status: a 10-year follow-up of men in the Whitehall II Study. Psychosom Med 63: 737–743.

Chauhan B, Mathias CJ, Critchley HD (2008). Autonomic contributions to empathy: evidence from patients with primary autonomic failure. Auton Neurosci 140: 96–100.

Coricelli G, Critchley HD, Joffily M et al. (2005). Regret and its avoidance: a neuroimaging study of choice behavior. Nat Neurosci 8: 1255–1262.

Craig AD (2002). How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3: 655–666.

Craig AD (2003). Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13: 500–505.

Craig AD (2005). Forebrain emotional asymmetry: a neuroanatomical basis? Trends Cogn Sci 9: 566–571.

Critchley HD (2004). The human cortex responds to an interoceptive challenge. Proc Natl Acad Sci U S A 101: 6333.

Critchley HD (2009). Psychophysiology of neural cognitive and affective integration: fMRI and autonomic indicants. Int J Psychophysiol 73: 88–94.

Critchley H, Corfield D, Chandler M et al. (2000a). Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. J Physiol 523: 259–270.

Critchley HD, Elliott R, Mathias C et al. (2000b). Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. J Neurosci 20: 3033.

Critchley HD, Mathias CJ, Dolan RJ (2001a). Neural activity in the human brain relating to uncertainty and arousal during anticipation. Neuron 29: 537–545.

Critchley HD, Mathias CJ, Dolan RJ (2001b). Neuroanatomical basis for first- and second-order representations of bodily states. Nat Neurosci 4: 207–212.

Critchley HD, Melmed RN, Featherstone E et al. (2001c). Brain activity during biofeedback relaxation: a functional neuroimaging investigation. Brain 124: 1003–1012.

Critchley HD, Mathias CJ, Josephs O et al. (2003). Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126: 2139.

Critchley HD, Wiens S, Rotshtein P et al. (2004). Neural systems supporting interoceptive awareness. Nat Neurosci 7: 189–195.

Critchley HD, Rotshtein P, Nagai Y et al. (2005a). Activity in the human brain predicting differential heart rate responses to emotional facial expressions. Neuroimage 24: 751–762.

Critchley HD, Taggart P, Sutton PM et al. (2005b). Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. Brain 128: 75–85.

Critchley HD, Tang J, Glaser D et al. (2005c). Anterior cingulate activity during error and autonomic response. Neuroimage 27: 885–895.

Critchley HD, Lewis PA, Orth M et al. (2007). Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material. Psychosom Med 69: 17–22.

Damasio AR (1994). Descartes' error: emotion reason and the human brain. GP Putnam, New York.

Damasio AR (1999). The feeling of what happens: body and emotion in the making of consciousness. Harcourt Brace, New York.

Damasio AR, Tranel D, Damasio HC (1991a). Somatic markers and the guidance of behavior: theory and preliminary testing. In: HS Levin, HM Eisenberg, AL Benton (Eds.), Frontal Lobe Function and Dysfunction. Oxford University Press, New York.

Damasio H, Kuljis RO, Yuh W et al. (1991b). Magnetic resonance imaging of human intracortical structure in vivo. Cereb Cortex 1: 374–379.

Darwin C (1872). The Expression of the Emotions in Man and Animals [Sl]. Murray, London.

Deady DK, North NT, Allan D et al. (2010). Examining the effect of spinal cord injury on emotional awareness expressivity and memory for emotional material. Psychol Health Med 15: 406–419.

Dehaene S, Posner MI, Tucker DM (1994). Localization of a neural system for error detection and compensation. Psychol Sci 5: 303–305.

Deljanin Z, Rancic N, Tiodorovic B et al. (2007). Association of stressful life events with acute myocardial infarction in population in the city of Nis within the period from 1998–2000. Vojnosanit Pregl 64: 463–468.

Di Martino A, Ross K, Uddin LQ et al. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. Biol Psychiatry 65: 63–74.

Dolan RJ (2002). Emotion cognition and behavior. Science 298: 1191–1194.

Donadio V, Kallio M, Karlsson T et al. (2002). Inhibition of human muscle sympathetic activity by sensory stimulation. J Physiol 544: 285–292.

Donadio V, Liguori R, Elam M et al. (2007). Arousal elicits exaggerated inhibition of sympathetic nerve activity in phobic syncope patients. Brain 130: 1653–1662.

Edwards L, McIintyre D, Carroll D et al. (2003). Effects of artificial and natural baroreceptor stimulation on nociceptive responding and pain. Psychophysiology 40: 762–769.

Eickhoff SB, Lotze M, Wietek B et al. (2006). Segregation of visceral and somatosensory afferents: an fMRI and cytoarchitectonic mapping study. Neuroimage 31: 1004–1014.

Ekman P, Friesen WV (1971). Constants across cultures in the face and emotion. J Pers Soc Psychol 17: 124–129.

Ekman P, Sorenson ER, Friesen WV (1969). Pan-cultural elements in facial displays of emotion. Science 1644: 86–88.

Ekman P, Levenson RW, Friesen WV (1983). Autonomic nervous system activity distinguishes among emotions. Science 2211: 1208–1210.

Fredrikson M, Furmark T, Olsson MT et al. (1998). Functional neuroanatomical correlates of electrodermal activity: a positron emission tomographic study. Psychophysiology 355: 179–185.

Frith C (2012). Explaining delusions of control: the comparator model 20 years on. Conscious Cogn 21: 52–54.

Fukushima H, Terasawa Y, Umeda S (2011). Association between interoception and empathy: evidence from heartbeat-evoked brain potential. Int J Psychophysiol 799: 259–265.

Georgiadis JR, Reinders AA, Paans AM et al. (2009). Men versus women on sexual brain function: prominent differences during tactile genital stimulation but not during orgasm. Hum Brain Mapp 300: 3089–3101.

Gianaros PJ, Van Der Veen FM, Jennings JR (2004). Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: implications for the cortical and subcortical regulation of cardiac autonomic activity. Psychophysiology 411: 521–530.

Gianaros PJ, Derbyshire SW, May JC et al. (2005). Anterior cingulate activity correlates with blood pressure during stress. Psychophysiology 422: 627–635.

Gianaros PJ, Horenstein JA, Cohen S et al. (2007a). Perigenual anterior cingulate morphology covaries with perceived social standing. Soc Cogn Affect Neurosci 22: 161–173.

Gianaros PJ, Jennings JR, Sheu LK et al. (2007b). Heightened functional neural activation to psychological stress covaries with exaggerated blood pressure reactivity. Hypertension 499: 134–140.

Gianaros PJ, Sheu LK, Matthews KA et al. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation volume and functional connectivity of the amygdala. J Neurosci 288: 990–999.

Gianaros PJ, Hariri AR, Sheu LK et al. (2009). Preclinical atherosclerosis covaries with individual differences in reactivity and functional connectivity of the amygdala. Biol Psychiatry 655: 943–950.

Gianaros PJ, Onyewuenyi IC, Sheu LK et al. (2012). Brain systems for baroreflex suppression during stress in humans. Hum Brain Mapp 33: 1700–1716.

Gray MA, Harrison NA, Wiens S et al. (2007a). Modulation of emotional appraisal by false physiological feedback during fMRI. PLoS One 22: E546.

Gray MA, Taggart P, Sutton PM et al. (2007b). A cortical potential reflecting cardiac function. Proc Natl Acad Sci U S A 1044: 6818–6823.

Gray MA, Minati L, Harrison NA et al. (2009). Physiological recordings: basic concepts and implementation during functional magnetic resonance imaging. Neuroimage 477: 1105–1115.

Gray M, Nagai Y, Critchley HD (Eds.), (2010a). Brain Imaging of Stress and Cardiovascular Responses. Springer-Verlag, London Limited.

Gray MA, Minati L, Paoletti G et al. (2010b). Baroreceptor activation attenuates attentional effects on pain-evoked potentials. Pain 1511: 853–861.

Gray MA, Beacher FD, Minati L et al. (2012). Emotional appraisal is influenced by cardiac afferent information. Emotion 12: 180–191.

Griffin MG, Resick PA, Mechanic MB (1997). Objective assessment of peritraumatic dissociation: psychophysiological indicators. Am J Psychiatry 1544: 1081–1088.

Groen Y, Wijers AA, Mulder LJ et al. (2007). Physiological correlates of learning by performance feedback in children: a study of EEG event-related potentials and evoked heart rate. Biol Psychol 766: 174–187.

Hajcak G, Mcdonald N, Simons RF (2003). To err is autonomic: error-related brain potentials and activity and post-error compensatory behavior. Psychophysiology 400: 895–903.

Harper RM, Bandler R, Spriggs D et al. (2000). Lateralized and widespread brain activation during transient blood pressure elevation revealed by magnetic resonance imaging. J Comp Neurol 4177: 195–204.

Harrison NA, Singer T, Rotshtein P et al. (2006). Pupillary contagion: central mechanisms engaged in sadness processing. Soc Cogn Affect Neurosci 11: 5–17.

Harrison NA, Wilson CE, Critchley HD (2007). Processing of observed pupil size modulates perception of sadness and predicts empathy. Emotion 77: 724–729.

Harrison NA, Brydon L, Walker C et al. (2009). Neural origins of human sickness in interoceptive responses to inflammation. Biol Psychiatry 666: 415–422.

Harrison NA, Gray MA, Gianaros PJ et al. (2010). The embodiment of emotional feelings in the brain. J Neurosci 300: 12878–12884.

Harrison NA, Kreibig S, Critchley HD (2011). Physiology of Emotion Responses. Handbook of Human Affective Neuroscience, Cambridge University Press, Cambridge.

Heaver B, Hutton SB (2011). Keeping an eye on the truth? Pupil size changes associated with recognition memory. Memory 199: 398–405.

Heims HC, Critchley HD, Martin NH et al. (2006). Cognitive functioning in orthostatic hypotension due to pure autonomic failure. Clin Auton Res 166: 113–120.

Hilton SM (1975). Ways of viewing the central nervous control of the circulation – old and new. Brain Res 877: 213–219.

Hobday DI, Aziz Q, Thacker N et al. (2001). A study of the cortical processing of ano-rectal sensation using functional MRI. Brain 1244: 361–368.

Kapur S (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160: 13–23.

Katkin ES, Wiens S, Ohman A (2001). Nonconscious fear conditioning visceral perception and the development of gut feelings. Psychol Sci 122: 366–370.

King AB, Menon RS, Hachinski V et al. (1999). Human forebrain activation by visceral stimuli. J Comp Neurol 4133: 572–582.

Kloner RA, Poole WK, Perritt RL (1999). When throughout the year is coronary death most likely to occur? A 12-year population-based analysis of more than 220 000 cases. Circulation 1000: 1630–1634.

Koponen H, Alaraisanen A, Saari K et al. (2008). Schizophrenia and sudden cardiac death: a review. Nord J Psychiatry 622: 342–345.

Krantz DS, Manuck SB (1984). Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull 966: 435–464.

Kreibig SD (2010). Autonomic nervous system activity in emotion: a review. Biol Psychol 844: 394–421.

Kring AM, Moran EK (2008). Emotional response deficits in schizophrenia: insights from affective science. Schizophr Bull 344: 819–834.

Kroes MC, Strange BA, Dolan RJ (2010). Beta-adrenergic blockade during memory retrieval in humans evokes a sustained reduction of declarative emotional memory enhancement. J Neurosci 300: 3959–3963.

Kuhn S, Gallinat J (2011). A quantitative meta-analysis on cue-induced male sexual arousal. J Sex Med 88: 2269–2275.

Labar KS, Ledoux JE, Spencer DD et al. (1995). Impaired fear conditioning following unilateral temporal lobectomy in humans. J Neurosci 155: 6846–6855.

Labar KS, Gatenby JC, Gore JC et al. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. Neuron 200: 937–945.

Lacey BC, Lacey JI (1978). Two-way communication between the heart and the brain. Significance of time within the cardiac cycle. Am Psychol 333: 99–113.

Lacey BC, Lacey JI (1980). Presidential Address 1979. Cognitive modulation of time-dependent primary bradycardia. Psychophysiology 177: 209–221.

Lader M (1975). The Psychophysiology of Mental Illness [SL], Routledge Kegan Paul, London.

Lane RD, Schwartz GE (1987). Induction of lateralized sympathetic input to the heart by the CNS during emotional arousal: a possible neurophysiologic trigger of sudden cardiac death. Psychosom Med 499: 274–284.

Lang PJ, Bradley MM, Cuthbert BN (1990). Emotion attention and the startle reflex. Psychol Rev 977: 377–395.

Lange CG, James W (1967). The Emotions. (Ed. Knight Dunlap), Hafner Publishing, New York.

Latalova K, Prasko J, Diveky T et al. (2010). Autonomic nervous system in euthymic patients with bipolar affective disorder. Neuro Endocrinol Lett 311: 829–836.

Leor J, Poole WK, Kloner RA (1996). Sudden cardiac death triggered by an earthquake. N Engl J Med 3344: 413–419.

Levenson RW (1992). Autonomic nervous system differences among emotions. Psychol Sci 33: 23.

Lorenz MW, Markus HS, Bots ML et al. (2007). Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 1155: 459–467.

Mathias CJ (2003). Autonomic diseases: clinical features and laboratory evaluation. J Neurol Neurosurg Psychiatry 7 (Suppl 3): iii31–iii41.

Matthews SC, Paulus MP, Simmons AN et al. (2004). Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. Neuroimage 222: 1151–1156.

Mauss IB, Robinson MD (2009). Measures of emotion: a review. Cognit Emot 233: 209–237.

Mayer-Gross W (1935). On depersonalization. British Journal of Medical Psychology 15: 103–122.

Medford N, Critchley HD (2010). Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct Funct 2144: 535–549.

Menon V, Uddin LQ (2010). Saliency switching attention and control: a network model of insula function. Brain Struct Funct 2144: 655–667.

Mittleman MA, Maclure M, Sherwood JB et al. (1995). Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators. Circulation 922: 1720–1725.

Mittleman MA, Maclure M, Nachnani M et al. (1997). Educational attainment anger and the risk of triggering myocardial infarction onset. The Determinants of Myocardial Infarction Onset Study Investigators. Arch Intern Med 1577: 769–775.

Moller J, Theorell T, De Faire U et al. (2005). Work related stressful life events and the risk of myocardial infarction case-control and case-crossover analyses within the Stockholm Heart Epidemiology Programme (SHEEP). J Epidemiol Community Health 599: 23–30.

Morgan HL, Turner DC, Corlett PR et al. (2011). Exploring the impact of ketamine on the experience of illusory body ownership. Biol Psychiatry 699: 35–41.

Morris AL, Cleary AM, Still ML (2008). The role of autonomic arousal in feelings of familiarity. Conscious Cogn 177: 1378–1385.

Nagai Y, Critchley HD, Featherstone E et al. (2004a). Brain activity relating to the contingent negative variation: an fMRI investigation. Neuroimage 211: 1232–1241.

Nagai Y, Critchley HD, Featherstone E et al. (2004b). Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a "default mode" of brain function. Neuroimage 222: 243–251.

Naqvi N, Shiv B, Bechara A (2006). The role of emotion in decision making. Curr Dir Psychol Sci 155: 260.

Nicotra A, Critchley HD, Mathias CJ et al. (2006). Emotional and autonomic consequences of spinal cord injury explored using functional brain imaging. Brain 1299: 718–728.

Nieuwenhuis S, Ridderinkhof KR, Blom J et al. (2001). Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. Psychophysiology 388: 752–760.

O'Connor MF, Gundel H, Mcrae K et al. (2007). Baseline vagal tone predicts bold response during elicitation of grief. Neuropsychopharmacology 322: 2184–2189.

Parvizi J, Anderson SW, Martin CO et al. (2001). Pathological laughter and crying: a link to the cerebellum. Brain 1244: 1708–1719.

Patterson JC 2nd, Ungerleider LG, Bandettini PA (2002). Task-independent functional brain activity correlation with skin conductance changes: an fMRI study. Neuroimage 177: 1797–1806.

Paulus MP, Stein MB (2006). An insular view of anxiety. Biol Psychiatry 600: 383–387.

Paus T, Koski L, Caramanos Z et al. (1998). Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior cingulate cortex: a review of 107 PET activation studies. Neuroreport 99: R37–R47.

Peled A, Ritsner M, Hirschmann S et al. (2000). Touch feel illusion in schizophrenic patients. Biol Psychiatry 488: 1105–1108.

Phillips DP, Jarvinen JR, Abramson IS et al. (2004). Cardiac mortality is higher around Christmas and New Year's than at any other time: the holidays as a risk factor for death. Circulation 1100: 3781–3788.

Pochon JB, Riis J, Sanfey AG et al. (2008). Functional imaging of decision conflict. J Neurosci 288: 3468–3473.

Pollatos O, Schandry S (2008). Emotional processing and emotional memory are modulated by interoceptive awareness. Cognit Emot 22: 272–287.

Raichle ME, Macleod AM, Snyder AZ et al. (2001). A default mode of brain function. Proc Natl Acad Sci U S A 988: 676–682.

Rainville P, Bechara A, Naqvi N et al. (2006). Basic emotions are associated with distinct patterns of cardiorespiratory activity. Int J Psychophysiol 611: 5–18.

Reedman LA, Allegra JR, Cochrane DG (2008). Increases in heart failure visits after Christmas and New Year's day. Congest Heart Fail 144: 307–309.

Roberts AC (2006). Primate orbitofrontal cortex and adaptive behaviour. Trends Cogn Sci 100: 83–90.

Schachter S, Singer JE (1962). Cognitive social and physiological determinants of emotional state. Psychol Rev 699: 379–399.

Schandry R (1981). Heart beat perception and emotional experience. Psychophysiology 188: 483–488.

Scherer KR (2000). Psychological models of emotion. In: JC Borod (Ed.), The Neuropsychology of Emotion. Oxford University Press, Oxford.

Schoofs D, Preuss D, Wolf OT (2008). Psychosocial stress induces working memory impairments in an n-back paradigm. Psychoneuroendocrinology 333: 643–653.

Shiv B, Loewenstein G, Bechara A (2005a). The dark side of emotion in decision-making: when individuals with decreased emotional reactions make more advantageous decisions. Brain Res Cogn Brain Res 233: 85–92.

Shiv B, Loewenstein G, Bechara A et al. (2005b). Investment behavior and the negative side of emotion. Psychol Sci 166: 435–439.

Singer T, Critchley HD, Preuschoff K (2009). A common role of insula in feelings empathy and uncertainty. Trends Cogn Sci 133: 334–340.

Smith CA, Ellsworth PC (1985). Patterns of cognitive appraisal in emotion. J Pers Soc Psychol 488: 813–838.

Stemmler G (Ed.), (2004). Physiological Processes During Emotion. Lawrence Erlbaum, Mahwah, NJ.

Stemmler G, Aue T, Wacker J (2007). Anger and fear: separable effects of emotion and motivational direction on somatovisceral responses. Int J Psychophysiol 666: 141–153.

Steptoe A, Strike PC, Perkins-Porras L et al. (2006). Acute depressed mood as a trigger of acute coronary syndromes. Biol Psychiatry 600: 837–842.

Stern ER, Gonzalez R, Welsh RC et al. (2009). Neural correlates of uncertainty during decision making in obsessive compulsive disorder. Biol Psychiatry 65: 125S.

Strike PC, Perkins-Porras L, Whitehead DL et al. (2006). Triggering of acute coronary syndromes by physical exertion and anger: clinical and sociodemographic characteristics. Heart 922: 1035–1040.

Suzuki S, Sakamoto S, Miki T et al. (1995). Hanshin-Awaji earthquake and acute myocardial infarction. Lancet 3455: 981.

Taggart P, Sutton P, Redfern C et al. (2005). The effect of mental stress on the non-dipolar components of the T wave: modulation by hypnosis. Psychosom Med 677: 376–383.

Thayer JF, Lane RD (2007). The role of vagal function in the risk for cardiovascular disease and mortality. Biol Psychol 744: 224–242.

Treiber FA, Kamarck T, Schneiderman N et al. (2003). Cardiovascular reactivity and development of preclinical and clinical disease states. Psychosom Med 655: 46–62.

Tsakiris M, Tajadura-Jimenez A, Costantini M (2011). Just a heartbeat away from one's body: interoceptive sensitivity predicts malleability of body-representations. Proc Biol Sci 2788: 2470–2476.

Van Stegeren AH, Everaerd W, Cahill L et al. (1998). Memory for emotional events: differential effects of centrally versus peripherally acting beta-blocking agents. Psychopharmacology (Berl) 1388: 305–310.

Vlastelica M (2008). Emotional stress as a trigger in sudden cardiac death. Psychiatr Danub 200: 411–414.

Wager TD, Van Ast VA, Hughes BL et al. (2009a). Brain mediators of cardiovascular responses to social threat. Part II. Prefrontal-subcortical pathways and relationship with anxiety. Neuroimage 477: 836–851.

Wager TD, Waugh CE, Lindquist M et al. (2009b). Brain mediators of cardiovascular responses to social threat. Part I. Reciprocal dorsal and ventral sub-regions of the medial prefrontal cortex and heart-rate reactivity. Neuroimage 477: 821–835.

Wallin BG (2007). Interindividual differences in muscle sympathetic nerve activity: a key to new insight into cardiovascular regulation? Acta Physiol (Oxf) 1900: 265–275.

Werner NS, Peres I, Duschek S et al. (2010). Implicit memory for emotional words is modulated by cardiac perception. Biol Psychol 855: 370–376.

Whitehead WE, Drescher VM (1980). Perception of gastric contractions and self-control of gastric motility. Psychophysiology 177: 552–558.

Whitehead WE, Drescher VM, Heiman P et al. (1977). Relation of heart-rate control to heartbeat perception. Biofeedback Self Regul 22: 371–392.

Wiens S, Mezzacappa ES, Katkin ES (2000). Heartbeat detection and the experience of emotions. Cognit Emot 144: 417–427.

Williams LM, Brammer MJ, Skerrett D et al. (2000). The neural correlates of orienting: an integration of fMRI and skin conductance orienting. Neuroreport 111: 3011–3015.

Willich SN, Maclure M, Mittleman M et al. (1993). Sudden cardiac death. Support for a role of triggering in causation. Circulation 877: 1442–1450.