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Interactions between visceral afferent signaling and stimulus processing

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Abstract

Visceral afferent signals to the brain influence thoughts, feelings and behaviour. Here we highlight the findings of a set of empirical investigations in humans concerning body-mind interaction that focus on how feedback from states of autonomic arousal shapes cognition and emotion. There is a longstanding debate regarding the contribution of the body, to mental processes. Recent theoretical models broadly acknowledge the role of (autonomically-mediated) physiological arousal to emotional, social and motivational behaviours, yet the underlying mechanisms are only partially characterized. Neuroimaging is overcoming this shortfall; first, by demonstrating correlations between autonomic change and discrete patterns of evoked, and task-independent, neural activity; second, by mapping the central consequences of clinical perturbations in autonomic response and; third, by probing how dynamic fluctuations in peripheral autonomic state are integrated with perceptual, cognitive and emotional processes. Building on the notion that an important source of the brain's representation of physiological arousal is derived from afferent information from arterial baroreceptors, we have exploited the phasic nature of these signals to show their differential contribution to the processing of emotionally-salient stimuli. This recent work highlights the facilitation at neural and behavioral levels of fear and threat processing that contrasts with the more established observations of the inhibition of central pain processing during baroreceptors activation. The implications of this body-brain-mind axis are discussed.

Overview

Neuroimaging, notably using nuclear magnetic resonance imaging (fMRI), has transformed human neuroscience over the last 20 years. Functional neuroimaging enables non-invasive *in vivo* evaluation of brain regions and networks supporting perceptions thoughts, feelings and continues to provide profound insight into normative brain mechanisms and functions. Neuroimaging findings have great translational potential, but so far clinical imaging biomarkers are largely limited to neurodegenerative conditions. Within autonomic neuroscience, the full impact of neuroimaging has yet to be realized. Arguably, the field has been restrained by technical challenges, for example in combining functional magnetic resonance imaging (fMRI) with detailed autonomic recording or associated experimental manipulations. However, such difficulties can and have been overcome (Gray et al. 2009a). Perhaps as relevant is a historical cultural stance that has rather underplayed the integration, across the neuraxis, of dynamic autonomic control and its contribution to perceptual, cognitive, motivational and volitional processes. This stance is increasingly challenged by neuroscientific findings and the pragmatics of therapeutic interventions. Here we review an area of autonomic neuroscience that combines human behavioural studies and neuroimaging to characterize the interaction between visceral physiology, perception and affect.

Historical background

The contribution of bodily arousal to thoughts and feelings has been debated for many centuries. The classical Greek physician Hippocrates and his followers, seemingly arguing against an existing doctrine, proposed that the

> *"..source of our pleasure, merriment, laughter and amusement, as of our grief, pain, anxiety and tears, is none other than the brain....(it) enables us to think, see and hear, and to distinguish the ugly and the beautiful, the bad and the good, pleasant and unpleasant…diaphragm nor heart.. neither take part in mental operations"* (Hippocrates 400 BCE)

Relatively soon afterwards a distinct, extreme alternative is attributed to Aristotle:

> *"..the brain is not responsible for any of the sensations.. the correct view [is] that the seat and source of sensation is the region of the heart….the motions of pleasure and pain, and generally all sensation plainly have their source in the heart.."*(Aristotle 350 BCE)

Despite Aristotelian dominance over Western European (church-led) thought, the brain re-emerged as in the distinction between 'hot' passion and 'cold' reason. With Descartes, the body (including the brain) was further distanced from cognitions, and seemingly it was not until Darwin systematically highlighted the commonalities across species in the physical, physiological and behavioural expression of emotions that the link between bodily states and emotional feelings was established once again in psychological thinking (Darwin 1872). At the turn of the 19th century, William James and Carl Lange both argued, with some differences, that emotional feeling states originated in physiological responses in the body:

> *"..that the bodily changes follow directly the perception of the exciting fact, and that our feeling of the same changes as they occur is the emotion*." (James 1884)

Lange in particular attributed both positive and negative emotions to visceral vasomotor reactions (Lange 1885/1912). Over the course of the 20th century, there followed a series of evaluations and critiques of physiological accounts of emotion, including, for example, quantifying emotional effects of parentral adrenaline administration, from Maranon and Cantril and Hunt, to Schacter and Singer (Cantril and Hunt 1932; Maranon 1924; Schachter and Singer 1962). Schachter and Singer's two stage model of emotion, followed Walter Cannon's dismissal of the contribution of peripheral physiology to emotional experience as epiphenomenological (Cannon 1927; Cannon 1931). Schachter and Singer's model represented a compromise that acknowledged a primary, yet non-specific contribution of physiological arousal to emotions, shaped into and labeled as particular emotion types by cognitive and social expectations (Schachter and Singer 1962). Over subsequent years, physiology has featured in both labelled line (dedicated function-specific) (e.g. Ekman et al. 1983; LeDoux 2000) and constructivist models of emotion (e.g. Barrett 2006; Damasio 1999).

Our own laboratory has attempted to combine cognitive neuroscience with clinical autonomic research, initially to test ideas put forward by Damasio and colleagues (Bechara and Damasio 2005; Bechara et al. 1997; Damasio et al. 1991) concerning the influence of peripheral physiological states on decisions, thoughts and feelings. These studies combined functional neuroimaging (first using positron emission tomography, PET, then magnetic resonance imaging) with monitoring of autonomic responses evoked by performance of cognitive emotional or effortful tasks (Critchley et al. 2000a; Critchley et al. 2000b; Critchley et al. 2005a; Critchley et al. 2005b). Across experiments, a characteristic pattern of activity was associated with states of psycho-physiological arousal, generally irrespective of whether the participants were processing salient emotional information or performing demanding cognitive or effortful motor tasks. Such challenges commonly evoke an enhancement of activity within dorsal anterior cingulate cortex (extending caudally to mid cingulate) accompanied by bilateral mid to anterior insular cortex activity. Activity in these areas typically correlate with autonomic change; a shifts in sympathovagal balance (toward sympathetic arousal and parasympathetic withdrawal) whether measured by electrodermal activity, changes in pupil size, heart rate acceleration or heart rate variability (Critchley et al. 2002; Critchley et al. 2003; Critchley et al. 2005a; Critchley et al. 2005b). This correspondence with peripheral autonomic response provides an integrative account of why regions such as 'cognitive' anterior cingulate physiological activate when both mental and physiological resources are diverted to meet behavioural challenges. Observed attenuation of sympathetic arousal in patients with lesions affecting dorsal anterior/mid cingulate (Tranel 2000) during motor and cognitive effort further supports the notion that rostromedial cortex hosts a visceromotor centre that drives action-ready autonomic states of during psychological arousal. Interestingly, the ventromedial prefrontal cortex and subgenual cingulate region appears, across a number of experiments, to be 'antisympathetic' and/or parasympathetic: For example, the tonic level of sympathetic electrodermal arousal is negatively correlated with activity within this region (Nagai et al. 2004) (Figure 1), and correspondingly, correlations between high frequency heart rate variability (an index of parasympathetic cardiac control) and ventromedial prefrontal cortical activity are also observed. In an elegant illustration, Wager and colleagues showed that increases in heart rate induced by the stress of 'social evaluation' are independently predicted by increased activity within dorsal anterior cingulate and decreased activity within ventromedial prefrontal cortex (Wager et al. 2009). In contrast to anterior cingulate cortex, across different studies evidence points to a role of insular cortex in representing (mapping) states of autonomic arousal and visceral change (Critchley et al. 2004; Pollatos et al. 2007).

Figure 1 about here

A core aspect to stress-induced physiological arousal is the suppression of the normal baroreflex response, to allow heart rate and blood pressure to rise together. During experimental induction of psychological stress, activity within dorsal cingulate, bilateral insula, amygdala and dorsal brainstem (midbrain periaqueductal grey matter) predicted the magnitude of beat-by-beat baroreflex suppression (Gianaros et al. 2012). It is noteworthy that each of these regions is implicated, indicating that dynamic interaction between afferent and efferent axes of autonomic control extend beyond brainstem to forebrain (both subcortical and cortical) centres. The contribution of afferent autonomic feedback to the expression of physiological arousal in emotion is consistent with the observed neural correlates of mental stress. Both insular cortex and amygdala are sensitive to the presence of threat-induced autonomic responses: In a fear conditioning study that compared patients with autonomic failure to healthy controls, the absence of an autonomic response to threat stimuli was associated with attenuated activity within amygdala and mid insula. Insular cortical responses, in both mid and right anterior regions, were observed to reflect the further integration of physiological feedback with the conscious processing of the threat stimuli, achieved experimentally by comparing responses to supraliminal and subliminal conditioned threat stimuli between autonomic failure and control participants (Critchley et al. 2002).

The general observation that, in health, subliminal threat stimuli can evoke physiological arousal responses provides support for the automatic primacy of bodily responses to emotional experience. Such evidence is very relevant to peripheral theories of emotion, where the feedback of bodily response is proposed to be the basis for emotional feelings (Lange and James 1967), in contrast to a common process generating feelings and physiological change. The information fed back from the automatic bodily response can then guide perceptions and decisions as 'somatic markers' (Bechara and Damasio 2005; Bechara et al. 1997; Damasio et al. 1991). Within this theme, Katkin and colleagues conducted a study where participants were subliminally presented (using backward masking) two stimuli, one of which predicted the occurrence of a later shock. At each trial, during a delay following the stimulus presentation, the participant was asked to judge whether they thought they would receive a shock. Without conscious awareness to enable discrimination between the stimuli, participants should have, in theory, performed at chance on this 'trace conditioning' task. However, it was observed that some individuals, preselected as being 'interoceptively aware' based on their accurate performance of a heartbeat detection task, were able to estimate well above chance whether a subliminal stimulus was paired with a later shock (Katkin et al. 2001). The interpretation was that those individuals most sensitive to their bodily responses, i.e. able to access the arousal responses generated automatically by the subliminal threat, could effectively use that information in their decision-making.

Interoceptive ability

The measurement of individual differences in interoceptive sensitivity/accuracy has over the years gravitated toward heartbeat detections tasks. Correlations with other axes of interoception (e.g. gastric filling) have reassured people that the ability to perceive individual heartbeats at rest can lead to inferences about an individual's more general sensitivity to internal bodily responses and arguably, by extension, their impact on emotional processes. Heartbeat detection tasks include the 'Schandry task': counting heartbeats at rest over a fixed interval (comparing reported to actual number of heartbeats measured using

electrocardiography) (Schandry 1981) and the Whitehead/Katkin task where people judge the timing (synchronous or delayed) of external auditory or visual stimuli relative to the heart beats that triggered the stimuli (Katkin et al. 1983; Whitehead et al. 1977; Wiens and Palmer 2001). Neuroimaging studies (Critchley et al. 2004; Pollatos et al. 2007) associate performance on heartbeat detection tasks with engagement of right insular cortex in particular as a part of a wider network of regions including anterior cingulate cortex (Medford and Critchley 2010). These studies confirm a role for insula engagement in interoceptive processing, providing further insight into how emotional feeling states especially of anxiety, are supported within interoceptive representations (Critchley et al. 2004; Paulus and Stein 2006). Interestingly, the response of part of right anterior insula differed during a Whitehead Katkin task, both according to whether participants' attention is focused 'interoceptively' on their heartbeats or exteroceptively only on the quality of the auditory stimuli, and according to the timing of the external stimulus (presence or absence of a delay relative to heartbeat) (Critchley et al. 2004) (see Figure 2). This interaction suggests, at least for right anterior insular cortex, that there is a fine-grained integration of external sensory information with representation of individual heartbeats. Anterior insular cortex therefore responded to mismatched timing between internal and external signals.

Figure 2 about here

Insula and detection of interoceptive mismatch

Peripheral theories of emotion superficially appear to predict that interoceptive sensitivity would be associated with enhanced emotional responsivity and correspondingly increased vulnerability to emotional disorders, including clinical anxiety. While 'good heartbeat detectors' maybe over represented among anxiety patients, interceptive accuracy does not account sufficiently. Attention to, appraisal and expectation of physiological arousal states interact with awareness to fuel symptoms such as anxiety (Clark 1986; Garfinkel et al. 2015; Paulus and Stein 2010; Wild et al. 2008). Contrasting the effects of false and true physiological (heartbeat) feedback during an MRI study, Gray and colleagues (Gray et al. 2007) showed that processing and subjective rating of neutral faces was enhanced in the presence of false physiological arousal, consistent with the notion that; 'unattributed arousal' was assigned to an ambiguous cause: the presence of neutral facial expressions. Correspondingly, intrinsically arousing emotional faces did not show the same enhancement effect. This behavioral effect supports the idea that unexpected physiological arousal contributes to states of anxiety or feelings of threat by donating salience to coincidental potential causes. In this false feedback study, neuroimaging identified right anterior insular cortex and amygdala activity as mediating processing of interoceptive/ exteroceptive error evoked by the false feedback to predict the enhancement of perceived intensity of neutral faces.

These data point to the coupling of emotional states autonomic activity and feedback via insular regions. The processing of threat is attenuated in different in people with absent autonomic responses who show less engagement of insula and amygdala in response to threatening stimuli, moreover mid and anterior region of right insula link the representation of autonomic arousal to conscious awareness of the likely cause of the autonomic arousal in a manner consistent with the two stage model of emotion proposed by Schachter and Singer (Schachter and Singer 1962), wherein emotions are constructed from the interpretation of physiological change in the concurrent cognitive context. Individual differences in

interoceptive awareness (heartbeat detection) influences emotional reactivity, and again the insular cortex is the dominant regions substrate for consciously accessible interoceptive representation. A major role of insula in processing physiological change lies in the processing of the mismatch between perceived and inferred / expected bodily state in an attention- dependent manner. Here unattributed arousal can alter emotional appraisal of face stimuli (via insula & amygdala) in a manner that appears to enhance the salience and potentially threatening nature of 'ambiguous' neutral stimuli (Gray et al. 2007).

Baroreceptor signaling and cardiac timing

In discussing the contributions of bodily physiology the processing of stimuli and the generation emotional feelings, there appears at least in our view to be a primacy or dominance of feedback of cardiovascular influences. While some autonomic indices such as electrodermal responses or pupil size may be sensitive indicators of emotional / affective reactions, states of cardiovascular arousal, particularly strong fast heartbeats, are felt as potent influences on subjective emotion. What is noteworthy about the feedback from the heart and great vessels is that the signal is phasic, pulsing with each heartbeat. The cardiac cycle describes the phases of atrial and ventricular filling and discharge of blood from the heart into the wider circulation. With each systole, blood leaves the left ventricle into the aorta and carotids where stretch receptor in the vessel walls (baroreceptors) are activated. These signals are conveyed centrally to the brainstem via the vagus and glossopharyngeal cranial nerves. Within the medulla, these phasic signals are processed to inform the baroreflex, whereby blood pressure is controlled by the slowing of the heart (parasympathetic vagus) after strong heart beats and inhibition of muscle sympathetic nerve activity to attenuate vasoconstriction of vascular beds. Strong baroreceptor discharges are responded to by adaptive adjustments to maintain perfusion pressure. The same channel of afferent information flow from aortic / carotid sinus baroreceptors to the brain is presumed to be the basis of heartbeat detection and the feeling states of physiological arousal accompanying motor and emotional behaviours. We can explore experimentally the effects of this viscerosensory pathway on other perceptual and mental processes without necessarily changing the overall state of cardiovascular arousal, since baroreceptor signals occur in bursts and are quiet between heartbeats: A brief stimulus presented at systole is processed concurrently with aortic/ carotid baroreceptors signaling, while this is not the case for a stimulus presented at diastole (Lacey and Lacey 1970; Rau and Elbert 2001).

Heartbeat timing experiments

There is an established body of literature that has pursued this type of experiment, and associated theory. Broadly, the majority of these studies indicate that stimuli presented concurrently with baroreceptor activation (natural activation at systole) or augmented with external neck suction) appear to be inhibited. This is particularly the case of painful stimuli (e.g. brief electrocutaneous shock) where there is attenuation of pain evoked potentials, nociceptive motor and autonomic reflexes ad the perception of pain presented at the time of baroreceptor activations relative to quiescent periods (Dworkin et al. 1994; Edwards et al. 2002; McIntyre et al. 2006; McIntyre et al. 2008; Rau and Elbert 2001). Baroreceptor stimulation is reported to engender similar blunting on stimulus processing. The observations of Lacey and Lacey (Lacey and Lacey 1978; Lacey and Lacey 1970) with respect to these and related cardiac cycle effects (including cardiac deceleration in anticipation and orientation, and acceleration for action and response) led to the formulation of a general principle that heartbeat / baroreceptor stimulation is generally inhibitory, perhaps

representing a distracting stream of information when one needs to survey one's surroundings, but which can help facilitate motor behaviors, including fight and flight responses, in part by devaluing external distraction.

The conjunction of arterial baroreceptor activation and external sensory stimulation has revealed some interesting autonomic effects. For example, contrary to the notion that sympathetic activation is a general indicator of psychophysiological arousal, the sympathetic responses to an arousing electrocutaneous shock at systole are distinct between electrodermal measures and muscle sympathetic nerve activity: the shock evokes an sympathetic skin response (irrespective of timing relation to baroreceptor activation) but causes inhibition of the burst-firing of muscle sympathetic nerve bundles (Donadio et al. 2002; Wallin 2007). The predicted consequence is therefore a transient drop in blood pressure. This inhibition of muscle sympathetic nerves diminishes through habituation if the stimulus is repeated over ensuing systoles. Most interestingly, there is much less habituation in blood-phobic fainters (Donadio et al. 2007), suggesting a physiological signature underlying the propensity to faint, wherein the interaction of interoceptive signals from the heart with the processing of directly threatening stimuli is linked to a stereotyped emotional behavioural reaction.

Neural correlates of heartbeat timing effects on sensory processing

Certainly such observations indicate the modulatory influence of signals from the heart and great vessels on external stimulus processing. Moreover, the habituation effect and link to blood phobia suggest that these mechanisms involved supratentorial regions supporting expectation, attentional and emotion. A neuroimaging study exploring the brain subregions supporting interactions between electrocutaneous shock and baroreceptor activation / heart timing combined a number of physiological indices (including noninvasive beat-to-beat blood pressure) with event-related functional magnetic resonance imaging (Gray et al. 2009b). Compared to timing at diastole, electrocutaneous shocks delivered at systole were associated with a flattening of blood pressure response which was coupled to changes in the activity of mid pons, bilateral anterior insula, and right amygdala. Interestingly, while this activity within pons and insula was attenuated to stimuli presented at systole, the effect in amygdala went in the opposite direction: blood-pressure coupled activity in amygdala was greatest at systole (Fig 3). There was further evidence to link these effects to baroreflex control: individual differences in high–frequency heart rate variability (an index of parasympathetic cardiac control) particularly predicted the differential evoked activation of insula at systole compared to diastole. Trial-by-trial changes in heart rate variability measure were predicted by systole/diastole activity difference within periaqueductal gray matter and amygdala (Gray et al. 2009b). This study therefore provided evidence for integration across viscerosensory, affective and autonomic systems within the brain in response to a salience physical stimulus.

Figure 3 about here

Using electroencephalography, to extend earlier knowledge regarding baroreceptor influences on pain processing, Gray and colleagues modulated participants' expectation of painful shock with visual cues. Early components of pain-evoked potentials (eg N2) were not significantly affected by expectation or systole/diastole timing. However the magnitude of a later component (P2, occurring around 400ms after shock delivery and distributed across central and right lateral scalp regions) differentiated between expected and unexpected shocks presented at diastole. Baroreceptor activation (i.e. the timing stimuli at systole) abolished the

difference between expected and unexpected shock on this P2 component. This observation was consistent with a simple model that suggests this later component of pain processing is gated by attention, but furthermore the operation of this attentional gate is conditional upon a baroreceptor gate: i.e. signals from the heart and great vessels exert their influence at an attention-dependent stage that follows initial sensory mapping to brain (Gray et al. 2010). Thus, at least for pain (and there is evidence for other sensory stimuli), natural baroreceptor afferent effects on sensory processing appear to occur at a secondary stage after initial sensory representation. Of relevant interest, however, are the findings of a recent magnetoencephalographic (MEG) study, which showed that the magnitude of heartbeat evoked potentials (an index of cortical representation of signals from the heart and great vessels) did in fact predict whether or not a fine grained visual stimulus (low resolution circular grating) entered conscious awareness (Park et al. 2014). Nevertheless, this MEG study did not show a direct effect of systole/diastole timing on stimulus detection.

Heartbeat timing effects on emotional processing

The core observation that the processing of emotive (pain) stimuli are modulated / gated by the cardiac cycle led to the question as to whether other types of salient emotional stimuli would be changed in value by these phasic cardiac afferent signals. Emotional facial expressions have been widely used in emotion research and affective neuroscience to probes and engage brains systems accommodating both labelled lines theories of specific discrete emotions (Ekman and Cordaro 2011; Ekman and Friesen 1971) and more dimensional constructionist view about emotional processing (Barrett 2006). Comparing the effects of presenting brief, but nevertheless overt, pictures of different emotional faces at systole and diastole demonstrated modest differences (c.1.5%) in subsequent heart rate for disgust and happy stimuli, both showing greater slowing of heart rate to these facial expressions when processes at systole compare to diastole. No significant effects were seen for sad and neutral faces (Gray et al. 2012). Moreover for disgust expressions there was also significant change in ratings of emotional intensity (measured rather insensitively on a 5 point Likert scale). This study was conducted during simultaneous brain imaging with fMRI, which revealed an area of periaqueductal gray matter whose activity mirrored the cardiac timing effect on stimulus processing and negatively emotional predicted ratings. Specifically for disgust, there was a similar convergent effect within left mid orbitofrontal cortex (Gray et al. 2012). Thus phasic baroreceptor signals contribute the processing of some emotions, but it is noteworthy that this study did not examine fear stimuli. This oversight was remedied in a further set of studies, motivated by the possibility that the heart timing effect may have the potential to differentiate and help people with anxiety disorders and fear-related conditions such as phobia.

The observation of amygdala engagement in the pain study also contributed to the motivation for a study similar to that of Gray and colleagues (2012), but combining fMRI with the presentation of fearful and neutral facial expressions at different phases of the cardiac cycle (systole and late diastole). The presentation of fear face stimuli at systole compared to diastole evoked an enhancement of subjective perception of the emotion, with reported intensity ratings changing by around 6%. A trend in the opposite direction was noted for neutral faces, with intensity ratings enhanced slightly at diastole. This effect of heart timing on emotion perception was associated with bilateral engagement of amygdala, the magnitude of which, particularly for the right amygdala, correlated with individual differences in trait anxiety levels (Garfinkel et al. 2014).

In the same set of investigations, a further effect was noted: baroreceptor activation, (as inferred from timing stimuli at systole) enhanced the detection of threat signals (fear faces) but not of other emotions (Garfinkel et al. 2014). In a rapid serial visual presentation (RSVP, attentional blink paradigm), emotional faces presented among distracting masks (at the border of conscious awareness) are more likely to break through' to conscious awareness. This 'emotional attentional blink' effect shows that salience of affect-laden stimuli grabs attention at an early stage (Anderson and Phelps 2001). In a behavioural study, timing emotional faces to phases of the cardiac cycle, produced a significant facilitation of this attentional grab for fear faces presented at systole compared to diastole, but not for disgust happy or neutral faces (though notably there was a trend for detection of neutral faces to be better at diastole). The magnitude of change was noteworthy with around a 9% average shift in detecting fear faces at systole compared to diastole. Interestingly, not all of the healthy participants of the study demonstrated this average effect: 3/19 people showed no differences between systole and diastole for fear faces detection and, 2/19 showed small effects in the opposite direction. At the other extreme, 3 people showed 25% or greater improvement in detection of fear faces at systole (Garfinkel et al. 2014). This study on fear detection clearly enriches the picture presented above regarding the impact of heart signals on early sensory processing (Gray et al. 2009b; Park et al. 2014). In summary, the cardiac timing effects markedly and selectively influence the detection and emotional appraisal for fear signals, at least for facial expressions. The direction of these effects on fear processing is the opposite of what had previously been the generally received wisdom that baroreceptor afferent inputs are inhibitory to stimulus processing, and the opposite of what is observed for the more direct challenge of brief painful (electrocutaneous) stimuli The effects in the brain appear mediated through systems, notably the amygdala, known to be engaged in threat processing and its integration with afferent information regarding autonomic arousal.

Conclusions and future research

The notion that states of autonomic arousal contribute to emotional processing has a long history. Its relevance is particularly noted in appraisal models of emotion and incorporated into cognitive models of panic and anxiety. Inspirational work in the 1970's and 1980's highlighted a particular role of baroreceptor activation in conveying signals to the brain about the state of cardiovascular arousal, beyond its proximate role in the reflex control of blood pressure. Heart timing experiments (reinforced by studies employing external mechanical manipulation of baroreceptors) highlighted inhibitory effects on processing of stimuli, notably the processing of pain, as expressed in motor reflexes electrocortical responses and subjective judgments. Recent work, particularly from our own laboratory has highlighted opposite effects on the processing of fear signals of potential threat, notable facial expressions. Here baroreceptor activation facilitates the detection of fear and augments the attribution of emotional salience. Brain imaging of these effects has helped not only define the levels of visceroaffective integration within brain, but imaging has also identified objective markers and potential targets of intervention since these same areas are typically implicated in affective psychopathology, including the expression of anxiety disorders. It is therefore a goal of future research to explore and exploit these observations. Fundamentally using or manipulating the afferent signals from heart to enhance or diminish the detection and processing of affective stimuli has potential application for characterizing and stratifying patient groups for different anxiolytic treatment, but may provide a means of enhancing the interventions themselves, for example by integrating physiological signals with computerized cognitive behavioural therapies. More options may emerge as we learn more about the neurochemistry and functional architecture supporting these effects.

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Figure legends

Figure 1

Neural activity reflecting reducing tonic level of sympathetic electrodermal arousal. The figure panels illustrate data presented from Nagai et al., 2004.
A. Decreases in skin conductance level were associated with increased activity in the vmPFC and OFC this effect was independent of task in that they occurred irrespective of whether participants performed a biofeedback arousal or a biofeedback relaxation task.
B. Across all participants, activity within the subgenual cingulate region was associated with decreases in tonic skin conductance level.

Figure 2

Neural correlates for interoceptive processing. The figure panels illustrate data presented in Critchley et al., 2004.
A. Activity in the insula is enhanced during interoceptive attention relative to an exteroceptive control condition (i.e. trials where attention is directed to the heart vs. trials where attention is directed to the notes alone).
B. Neural activity reflecting the interaction between interoceptive/exteroceptive attention (heart vs. notes) and feedback delay (tones synchronous or delayed with respect to the heartbeat). For delayed stimuli, activity in right insula is enhanced during interoceptive focus and reduced during exteroceptive focus.

Figure 3

Neural activity reflecting interaction between cardiac afferent information within cardiac cycle and electrocutaneous shock processing. The figure panels illustrate data presented in Gray et al. 2009b. Electrocutaneous shocks administered at cardiac systole (around T wave of electrocardiogram; ECG) inhibit normal blood pressure response and are decrease blood pressure-related activity with insula and pons while increasing activity in amygdala (relative to diastole). **A.** Timing of electrocutaneous stimuli relative to ECG R-wave: aiming to trigger at systole around ECG T wave, and to trigger at diastole (immediate presystole period. In fact for practical purposes stimulus events were triggered in a predictive way from pulse oximetry data and the accuracy of relationship to concurrently recording ECG confirmed post hoc.
B. Group data illustrating the differential effect of shock timing in cardiac cycle on beat-to-beat mean arterial blood pressure responses across the group. Systole was observed to attenuate blood pressure increase to shock.
C.- E. Group BOLD activity tracking blood pressure following shock delivery was contrasted for events at systole versus diastole. Activity within **C.** bilateral insular cortex regions and **D.** dorsal brainstem (mid pons) was greater at diastole compared to systole. **E.** Group activity in right amygdala was greater at systole compared to diastole.

References

Anderson AK, Phelps EA. 2001. Lesions of the human amygdala impair enhanced perception of emotionally salient events. Nature 411(6835):305-309.

Aristotle. 350 BCE. Parts of Animals.

Barrett LF. 2006. Are Emotions Natural Kinds? Perspectives on Psychological Science 1(1):28-58.

Bechara A, Damasio AR. 2005. The somatic marker hypothesis: A neural theory of economic decision. Games and Economic Behavior 52(2):336-372.

Bechara A, Damasio H, Tranel D, Damasio AR. 1997. Deciding advantageously before knowing the advantageous strategy. Science 275(5304):1293-5.

Cannon WB. 1927. The James-Lange theory of emotions: A critical examination and an alternative theory. American Journal of Psychology 39:106-124.

Cannon WB. 1931. Again the James-Lange and the thalamic theories of emotion. Psychological Review 38:281-295.

Cantril H, Hunt WA. 1932. Emotional effects produced by the injection of adrenalin. American Journal of Psychology 44:300-307.

Clark DM. 1986. A cognitive approach to panic. Behav Res Ther 24(4):461-70.

Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. 2000a. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. Journal of Physiology-London 523(1):259-270.

Critchley HD, Elliott R, Mathias CJ, Dolan RJ. 2000b. Neural activity relating to generation and representation of galvanic skin conductance responses: A functional magnetic resonance imaging study. Journal of Neuroscience 20(8):3033-3040.

Critchley HD, Mathias CJ, Dolan RJ. 2002. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron 33(4):653-63.

Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ. 2003. Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126(Pt 10):2139-52.

Critchley HD, Rotshtein P, Nagai Y, O'Doherty J, Mathias CJ, Dolan RJ. 2005a. Activity in the human brain predicting differential heart rate responses to emotional facial expressions. Neuroimage 24(3):751-762.

Critchley HD, Tang J, Glaser D, Butterworth B, Dolan RJ. 2005b. Anterior cingulate activity during error and autonomic response. Neuroimage 27(4):885-895.

Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. 2004. Neural systems supporting interoceptive awareness. Nat Neurosci 7(2):189-95.

Damasio AR. 1999. The feeling of what happens : body and emotion in the making of consciousness. New York: Harcourt Brace. xii, 386 p. p.

Damasio AR, Tranel D, Damasio HC. 1991. Somatic markers and the guidance of behavior: theory and preliminary testing. In: Levin HS, Eisenberg HM, Benton AL, editors. Frontal lobe function and dysfunction: Oxford University Press. p xv,427p.

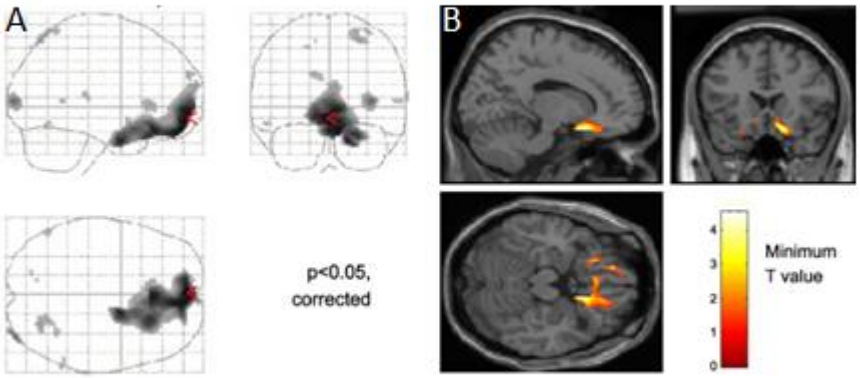
Darwin C. 1872. The expression of the emotions in man and animals. [S.l.]: Murray.

Donadio V, Kallio M, Karlsson T, Nordin M, Wallin BG. 2002. Inhibition of human muscle sympathetic activity by sensory stimulation. Journal of Physiology-London 544(1):285-292.

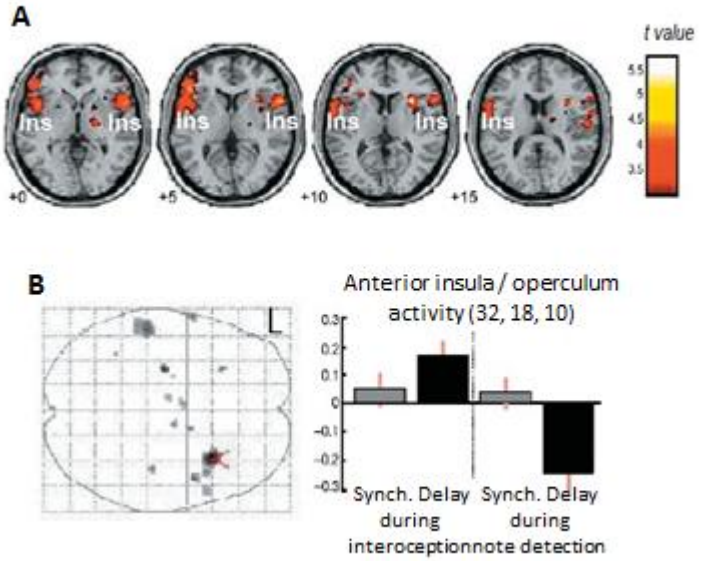
Donadio V, Liguori R, Elam M, Karlsson T, Montagna P, Cortelli P, Baruzzi A, Wallin BG. 2007. Arousal elicits exaggerated inhibition of sympathetic nerve activity in phobic syncope patients. Brain 130:1653-1662.
Dworkin BR, Elbert T, Rau H, Birbaumer N, Pauli P, Droste C, Brunia CHM. 1994. Central Effects of Baroreceptor Activation in Humans - Attenuation of Skeletal Reflexes and Pain Perception. Proceedings of the National Academy of Sciences of the United States of America 91(14):6329-6333.
Edwards L, McIntyre D, Carroll D, Ring C, Martin U. 2002. The human nociceptive flexion reflex threshold is higher during systole than diastole. Psychophysiology 39(5):678-681.
Ekman P, Cordaro D. 2011. What is Meant by Calling Emotions Basic. Emotion Review 3(4):364-370.
Ekman P, Friesen WV. 1971. Constants across cultures in the face and emotion. J Pers Soc Psychol 17(2):124-9.
Ekman P, Levenson RW, Friesen WV. 1983. Autonomic nervous system activity distinguishes among emotions. Science 221(4616):1208-10.
Garfinkel SN, Minati L, Gray MA, Seth AK, Dolan RJ, Critchley HD. 2014. Fear from the Heart: Sensitivity to Fear Stimuli Depends on Individual Heartbeats. Journal of Neuroscience 34(19):6573-6582.
Garfinkel SN, Seth AK, Barrett AB, Suzuki K, Critchley HD. 2015. Knowing your own heart: Distinguishing interoceptive accuracy from interoceptive awareness. Biological Psychology 104:65-74.
Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD. 2012. Brain systems for baroreflex suppression during stress in humans. Human Brain Mapping 33(7):1700-1716.
Gray MA, Beacher FD, Minati L, Nagai Y, Kemp AH, Harrison NA, Critchley HD. 2012. Emotional Appraisal Is Influenced by Cardiac Afferent Information. Emotion 12(1):180-191.
Gray MA, Harrison NA, Wiens S, Critchley HD. 2007. Modulation of Emotional Appraisal by False Physiological Feedback during fMRI. PLoS One 2(6).
Gray MA, Minati L, Harrison NA, Gianaros PJ, Napadow V, Critchley HD. 2009a. Physiological recordings: basic concepts and implementation during functional magnetic resonance imaging. Neuroimage 47(3):1105-15.
Gray MA, Minati L, Paoletti G, Critchley HD. 2010. Baroreceptor activation attenuates attentional effects on pain-evoked potentials. Pain 151(3):853-861.
Gray MA, Rylander K, Harrison NA, Wallin BG, Critchley HD. 2009b. Following One's Heart: Cardiac Rhythms Gate Central Initiation of Sympathetic Reflexes. Journal of Neuroscience 29(6):1817-1825.
Hippocrates. 400 BCE. On the Sacred Disease
James W. 1884. What is an Emotion? Mind 9(188-205).
Katkin ES, Reed SD, Deroo C. 1983. A Methodological Analysis of 3 Techniques for the Assessment of Individual-Differences in Heartbeat Detection. Psychophysiology 20(4):452-452.
Katkin ES, Wiens S, Ohman A. 2001. Nonconscious fear conditioning, visceral perception, and the development of gut feelings. Psychol Sci 12(5):366-70.
Lacey BC, Lacey JI. 1978. Two-way communication between the heart and the brain. Significance of time within the cardiac cycle. Am Psychol 33(2):99-113.

Lacey I, Lacey BC. 1970. Some autonomic-central nervous system interrelationships. In: Black P, editor. Physiological correlates of emotion. New York Academic Press. p 205–22.
Lange CG, editor. 1885/1912. The mechanisms of the emotions. Boston: Houghton Mifflin. 672–684 p.
Lange CG, James W. 1967. The Emotions. By Carl Georg Lange and William James, etc. (Edited by Knight Dunlap.-Reprinted.). Dunlap K, editor. New York ; London: Hafner Publishing Co. 135 p. p.
LeDoux JE. 2000. Emotion circuits in the brain. Annual Review of Neuroscience 23:155-184.
Maranon G. 1924. Contribution à l'étude de l'action émotive de l'adrénaline. Revue Francaise D'Endocrinologia 2(5):301-325.
McIntyre D, Edwards L, Ring C, Parvin B, Carroll D. 2006. Systolic inhibition of nociceptive responding is moderated by arousal. Psychophysiology 43(3):314-319.
McIntyre D, Kavussanu M, Ring C. 2008. Effects of arterial and cardiopulmonary baroreceptor activation on the upper limb nociceptive flexion reflex and electrocutaneous pain in humans. Pain 137(3):550-555.
Medford N, Critchley HD. 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct Funct 214(5-6):535-49.
Nagai Y, Critchley HD, Featherstone E, Trimble MR, Dolan RJ. 2004. Activity in ventromedial prefrontal cortex covaries with sympathetic skin conductance level: a physiological account of a "default mode" of brain function. Neuroimage 22(1):243-51.
Park HD, Correia S, Ducorps A, Tallon-Baudry C. 2014. Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nature Neuroscience 17(4):612-U178.
Paulus MP, Stein MB. 2006. An insular view of anxiety. Biol Psychiatry 60(4):383-7.
Paulus MP, Stein MB. 2010. Interoception in anxiety and depression. Brain Structure & Function 214(5-6):451-463.
Pollatos O, Schandry R, Auer DP, Kaufmann C. 2007. Brain structures mediating cardiovascular arousal and interoceptive awareness. Brain Res 1141:178-87.
Rau H, Elbert T. 2001. Psychophysiology of arterial baroreceptors and the etiology of hypertension. Biological Psychology 57(1-3):179-201.
Schachter S, Singer JE. 1962. Cognitive, social, and physiological determinants of emotional state. Psychol Rev 69:379-99.
Schandry R. 1981. Heart beat perception and emotional experience. Psychophysiology 18(4):483-8.
Tranel D, editor. 2000. Electrodermal activity in cognitive neuroscience: neuroanatomical
and neuropsychological correlates. New York: Oxford University Press. 92–224 p.
Wager TD, Waugh CE, Lindquist M, Noll DC, Fredrickson BL, Taylor SF. 2009. 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 47(3):821-35.
Wallin BG. 2007. Interindividual differences in muscle sympathetic nerve activity: a key to new insight into cardiovascular regulation? Acta Physiologica 190(4):265-275.
Whitehead WE, Drescher VM, Heiman P, Blackwell B. 1977. Relation of heart-rate control to heartbeat perception Biofeedback and Self-Regulation 2(4):371-392.

Wiens S, Palmer SN. 2001. Quadratic trend analysis and heartbeat detection. Biol Psychol 58(2):159-75.
Wild J, Clark DM, Ehlers A, McManus F. 2008. Perception of arousal in social anxiety: Effects of false feedback during a social interaction. Journal of Behavior Therapy and Experimental Psychiatry 39(2):102-116.



644 Fig 1
645


A
t value
5.5
5
4.5
4
3.5
Ins
Ins
Ins
Ins
Ins
Ins
Ins
+0
+5
+10
+15
B
L
Anterior insula / operculum
activity (32, 18, 10)
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
Synch. Delay during interoception
Synch. Delay during note detection

646 Fig 2
647

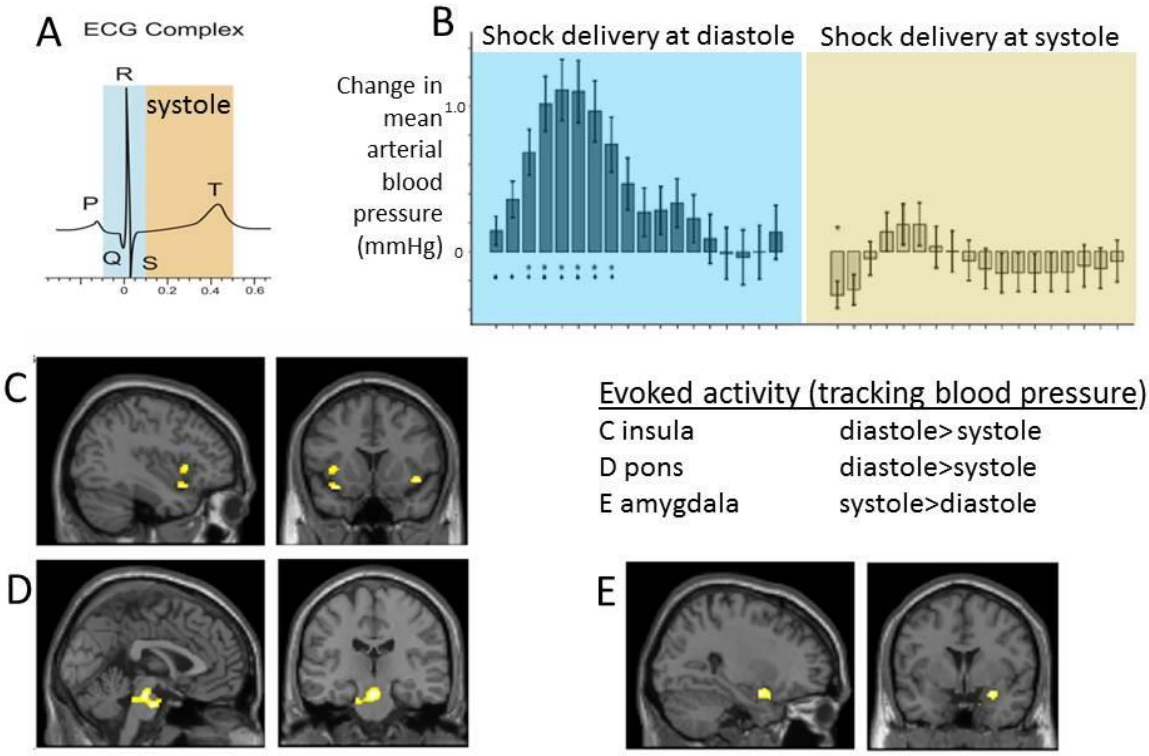

A
ECG Complex
R
systole
P
T
Q
S
0
0.2
0.4
0.6
B
Shock delivery at diastole
Shock delivery at systole
Change in mean arterial blood pressure (mmHg)
1.0
0
C
D
E
Evoked activity (tracking blood pressure)
C insula diastole> systole
D pons diastole>systole
E amygdala systole>diastole

Fig 3

Figure 1.JPEG

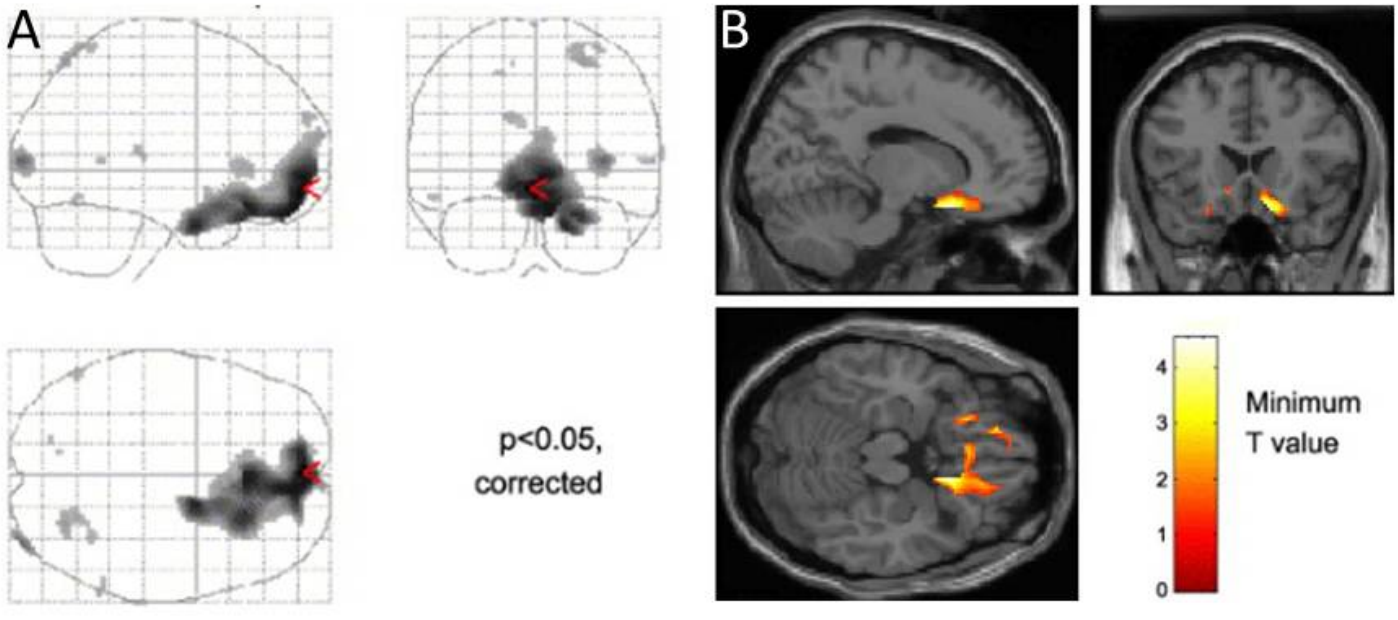


Figure 2.JPEG

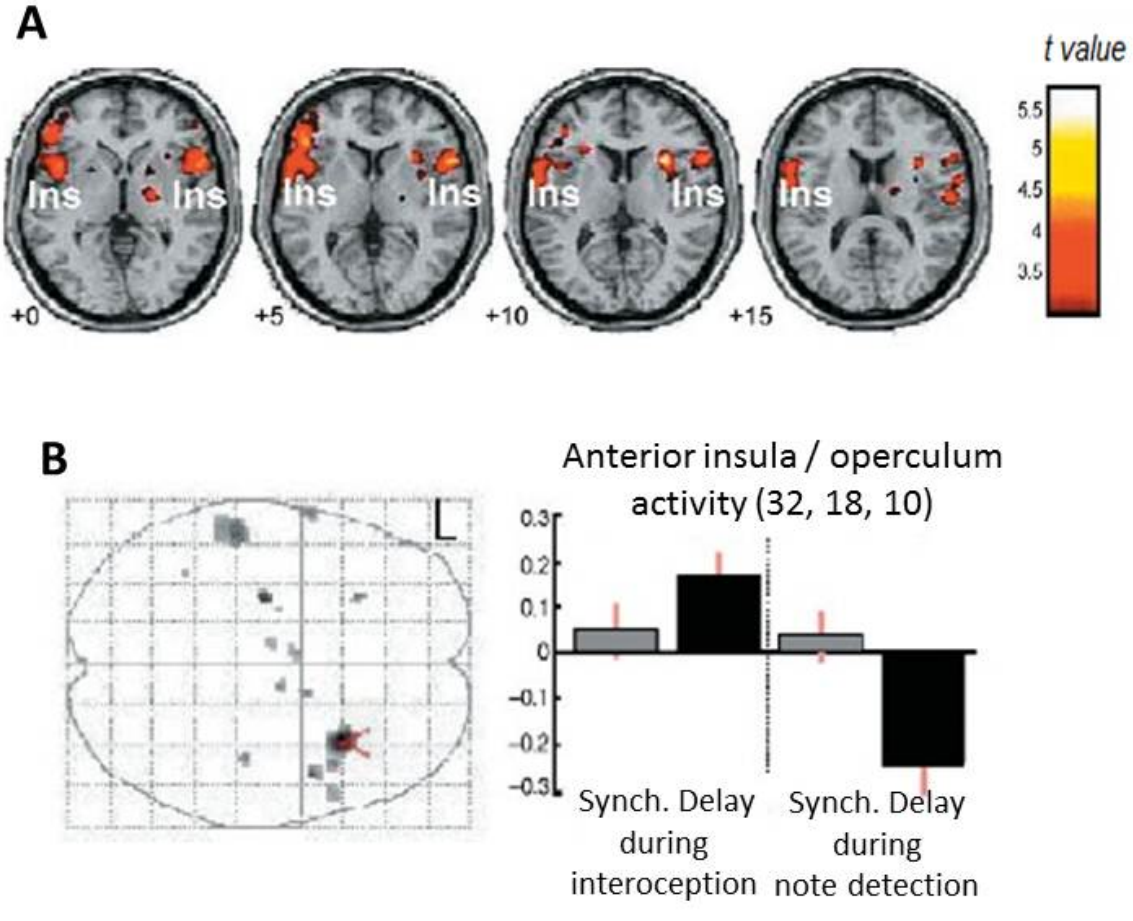


Figure 3.JPEG