Emotion and its disorders

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Emotional processes are crucial to the control of human behaviour and anchored to a common foundation in motivational mechanisms where emotional cues have intrinsic re-inforcement values. Emotions per se are transient events, produced in response to external or self-generated emotive stimuli, and typically characterized by attention to the stimulus, involuntary arousal reactions and changes in motor behaviour, subjective feeling states and subsequent biasing of behaviour. Primary emotions, such as happiness and fear, correspond motivationally with approach or withdrawal responses. In humans, feeling-states and subjective emotional experiences reflect cognitive contextual awareness of emotional responses and may be embellished into secondary emotions, such as guilt or relief. This review addresses the application of neuroimaging techniques to understanding the neural mechanisms supporting these aspects of emotional experience.

Processing of emotional cues

Processing of communicative emotional expressions

A rich vocabulary of communication exists in expressions of emotion as conveyed by changes in facial muscles, autonomic changes in skin and pupil, speech prosody, stance and movements. The ability to perceive and interpret emotional expressions is essential for adaptive social behaviour. Information from faces is particularly communicative. Neuroimaging experiments have identified a region of visual (fusiform) cortex selectively activated when processing faces. Connecting regions of lateral temporal association cortex are implicated in processing mouth movements and gaze-direction that contribute to processing emotional expressions. These specialized cortical representations of facial information connect to regions where emotional valence is extracted, or attributed to, face identity and expression. Functional neuroimaging evidence lends some support to the theoretical construct that emotional expressions are processed along distinct neural pathways that reflect motivational meaning. For example, amygdala activity is modulated by threatening stimuli, or by processing fearful (facial or vocal) expressions of others (Fig. 1A), whereas facial expressions of
disgust enhance activity in anterior insula and basal ganglia, anatomically related to autonomic and gustatory centres. Distinct processing streams allow for differing emotions to be coupled adaptively with distinct behavioural response repertoires and the visceromotor responses that facilitate them, e.g. freeze or escape in the presence of

Fig. 1 (A) Amygdala responses in the processing of fearful faces, in a PET study by Morris et al. Face stimuli were derived from the Ekman series of prototypical facial expressions, but electronically manipulated to provide a range of stimuli along the fearful/happy dimension. The greater the degree of fear expressed in the facial expression, the greater regional blood flow in left amygdala, associated with increased neural activity. (B) Amygdala responses to unseen fear. In another PET study by Morris et al. One of two angry faces (CS+) was conditioned to indicate threat through pairing with an aversive white noise, the other angry face (CS-) was not paired with any aversive stimulus. A backward masking procedure was used to present subliminally these faces: by rapidly presenting (30 ms) the CS+ or CS- face then covering it with a neutral face (45 ms), subjects see only the neutral face and are unaware that they saw an angry face. However, skin conductance responses (SCR) are nevertheless greater to the unseen CS+ compared to the unseen CS-. Greater activity in the right amygdala is also observed to the masked CS+ compared to the masked CS- face, consistent with emotional processing independent of awareness.
threat, exhale and vomit to contamination implicit in disgust. However, there is still uncertainty as to the extent of such neuro-anatomical segregation: Amygdala activity may increase to give expressions of happiness and sadness as well as fear

The Jamesian model of emotional processing is that of a reflex: An ‘exciting’ stimulus automatically elicits a motor or autonomic response (subjective emotional experience, or feeling state, is a secondary interpretation of bodily response that may be contextually influenced). The automatic ‘unconscious’ elicitation of emotion has been examined using functional imaging using subliminal presentation of face-stimuli (using backward masking and rapid presentation, the subject is not aware of the emotive stimulus; see Fig. 1). When an ‘unseen’ face represents a potential threat, the stimulus still evokes amygdala activation (and a bodily arousal response). A subcortical route is implicated in mediating this unconscious processing of emotional stimulus, by-passing temporal lobe and insula cortices associated with conscious awareness and detailed feature-processing of the stimuli. These observations provide key empirical evidence for a causal, automatic, link between stimulus and emotional response. The evidence for two processing pathways to amygdala is consistent with observations in animal experiments. Since survival is dependent on a rapid response, a fast (subcortical) pathway evokes alertness and escape behaviour to minimally processed, potentially threatening stimuli; a second pathway via cortex provides for a more detailed representation of the potential threat, enabling correction or reinforcement of the immediate fear response (Fig. 1B).

Stereotypical feature relationships underlie emotion-related processing of facial expression. Thus, line drawings of faces with happy and angry facial expressions are sufficient to evoke differential amygdala activity. The amygdala also responds differentially to upright versus inverted ‘Thatcher illusion faces’. In this model, a face can be made to look bizarre and ‘emotionally threatening’ by inverting facial features such as mouth and eyes. The emotional charge of the face is much reduced if the same manipulated face is presented upside-down, because component features are no longer processed within their global context. Differential amygdala activity to these manipulations indicate that a global integration of feature relationships is necessary for processing emotional facial expression.

In experiments examining auditory processing of emotional signals, low-level qualities, in this case prosody, are again the primary source of emotional information within speech. Non-speech intonations of emotional states (groans, squeals, etc) modulate activity to similar brain regions that are modulated by facial expressions of the same emotion, strengthening the evidence for emotional processing along distinct lines.
In summary, neuroimaging experiments suggest partial segregation of streams for the processing of communicative emotional signals. Such processing may occur independently of awareness, drawing from low-level global stimulus representations in addition to more detailed cortical processing of expression. The identification of dedicated cortical systems for detailed representations of faces and facial features which are coupled with both emotional responses and conscious awareness provides a further level at which communicative emotional signals may exert an influence on cognitive processing and social interactions.

**Processing of other emotive stimuli**

Complex environmental and social stimuli may evoke emotions by virtue of their direct or implicit motivational meanings. Facial cues, such as eye-gaze, beauty and more elusive judgements of social potential, also share the motivational properties of ‘primary re-inforcers’. The perception of attractive faces is associated with enhanced activity in ‘reward centres’, such as ventral striatum, which is maximal when eye gaze is directed at the viewer\(^\text{17}\). Interestingly, in ‘romantic love’, the face of a loved one evokes a pattern of striatal, cingulate and insular activity similar that associated with obsessive compulsive disorder\(^\text{18}\). Negative judgements of emotional attributes may evoke activity associated with implied threat, for example, faces rated by a viewer to be more ‘untrustworthy’ evoke greater amygdala activity, independent of attention to this facial quality\(^\text{19}\).

Complex visual scenes and even individual words may be rated according to emotive power or emotional content. A set of pictures, the International Affective Picture System (IAPS), comprises of a large range of scenes that vary in their emotional valence (positive and negative) and their evocation of subjective arousal. In a combined fMRI and MEG study, negative pictures activated medial orbitofrontal cortex whereas positive pictures preferentially activated lateral orbitofrontal cortex\(^\text{20}\). The MEG data indicated a more rapid processing of emotional pictures, particularly those with negative content, than non-emotional pictures. Amygdala responses are reportedly enhanced by emotional words and positive emotional words that also activate reward-related regions of ventral striatum\(^\text{7}\). In contrast, perception of humour is reported to activate medial prefrontal cortex\(^\text{21}\). In perhaps what is a canonical neuroimaging experiment of emotion, a recent fMRI study used a direct measure of sexual arousal as a regressor of interest when male subjects watched pornography or sport films. Regional activity within insula, basal ganglia and cingulate cortex, as well as visual and somatosensory cortices co-varied positively with sexual arousal\(^\text{22}\). It is noteworthy that much less activity was attributable to the stimuli themselves compared to activity directly correlated with physiological changes.
Pain, itch and tickle as emotional stimuli

Emotion (reflecting a contextual interpretation of valence) is an important contributing factor to the difference between strong somatosensory stimulation and pain, or even light touch and tickle. There is a detailed review of pain research by Jones²³. The presence of subjective pain is associated with consistently reported activity increases within the ‘pain matrix’. This set of regions includes hypothalamus and thalamus, somatosensory and parietal cortices and, importantly from the emotional perspective, also anterior cingulate, insula, lateral and medial prefrontal cortex²³,²⁴. Anterior cingulate cortex in particular may integrate painful experience with attention, arousal and subjective emotional state. However, even within anterior cingulate cortex, pain-related activity can be dissociated from activity related to stimulus intensity, implicating older, limbic cingulate regions in representations of pain²⁵.

Disorders of processing emotional stimuli

Neuropsychological studies of patients with focal brain lesions have provided the basis of understanding many brain processes involved in emotion and emotional disorder. On this foundation, neuroimaging research has added powerful insights into central correlates of disorders of emotion, even where structural changes in brain anatomy are not obviously apparent. For example, some of the social and emotional deficits associated with autism may partly derive from inattention to, or aberrant processing of, emotional stimuli, particularly communicative expressions. When processing emotional expressions, deficits in activity within amygdala²⁶,²⁷ and fusiform cortex²⁷ have been observed in people with autistic symptoms. Subtle structural morphometric abnormalities have been observed in autistic individuals in brain regions associated with processing of emotional cues, including amygdala, cingulate and lateral temporal cortex²⁸. Abnormal mechanisms in the processing of emotional cues are also proposed to underlie behavioural features of other ‘emotional’ disorders, such as developmental psychopathy²⁹ where amygdala dysfunction during processing of distress signals is implicated in this disorder of empathy.

Representation of internal feeling states

Subjective emotional states

Mood states have variously been induced in healthy subjects by presentations of emotional stimuli (such as facial expressions, emotive music, IAPS pictures, or subjective recall of emotional experiences) where
the subject is instructed to experience (and rate) with the depicted or remembered emotion. Attention to subjective mood state increases activity within rostral anterior cingulate. Subjective states of sadness, happiness and disgust induced by film or by recall have been associated with activation of medial prefrontal cortex and thalamus. Participation of somatosensory cortex and insula has also been observed during recollection emotional experiences, consistent with an importance of somatic representations to emotional feeling states. Negative mood states have been associated with increases in insula and amygdala activity, consistent with processing aversive material. Sadness has been associated with activity in anterior insula and happiness by subgenual cingulate activity. Symptom provocation in people with simple phobias or obsessive-compulsive disorder (OCD) have many similarities with mood induction studies and, in general, increased activity is observed in orbitofrontal cortex, insula, amygdala and basal ganglia, regions implicated in fear, aversion, arousal and compulsive responses.

Subjective emotional states can be directly experimentally manipulated to produce changes in emotional behaviour, attention and arousal. This may involve inducing motivational change (e.g. thirst or hunger) or employing selective neurochemical interventions that can target specifically emotional mechanisms. Tryptophan depletion, resulting in serotonergic dysfunction, can transiently depress an individual’s mood, which in turn is associated with decreased activity in anterior cingulate, orbitofrontal cortex and basal ganglia. In general, pharmacological interventions have been an under-used methodology to probe interactions between subjective emotion state and neurochemical mechanisms.

Feelings and arousal states

The role of bodily arousal states has been emphasized in many theories of emotion. Neuroimaging studies have tended to under-emphasize the observation that brain regions implicated in emotional processing are involved at some level in control of autonomic responses and peripheral arousal states. However, some studies have attempted to map directly regional brain activity associated with peripheral autonomic responses. These studies implicate anterior cingulate, medial prefrontal, and insula cortices in generation and representation states of autonomic arousal (Fig. 2). Moreover, these regions support interactions between autonomic activity and cognitive processing, for example during reward-anticipation, cognitive effort and stimulus awareness. Regional representations of bodily arousal, particularly where modulated by (experimental) context, may be the substrate of ‘feeling states’ and also mediate the influence of arousal on attentional processes.
Disorders of subjective emotional state and arousal

Affective (mood) disorders are characterized by feeling states: (i) depression by feelings of sadness; (ii) hypomania by feelings of elation; and (iii) happiness and anxiety disorders by fear. These mood disorders are also associated with changes in saliency of perceived cues, cognitive and mnemonic performance, motor and arousal states, which may confound interpretation of functional imaging experiments. Differences in brain morphology have been related to predisposition to mood disorder (for example, ventromedial prefrontal cortex abnormalities in forms of depression or anterior cingulate associations with anxiety). More
selective disorders of subjective feeling states may include paranoid feelings, depersonalization and somatization. In depersonalization disorder, a characteristic feature is a sense of emotional detachment. Functional imaging findings include reductions in activity with insula cortex, adjacent to areas implicated in integrating emotional awareness and arousal.

**Emotional and motivational learning**

*Primary re-inforcement and satiation*

Emotion is conceptually rooted in the processing of reward and punishment. Primary rewards satisfy intrinsic drives necessary for survival, and elicit positive emotional states. Proxy awards such as money, pictures of money, points score and tick marks share similar re-inforcing qualities in humans. Areas including orbitofrontal cortex and ventral striatum are activated by primary rewards such as pleasant tastes, and by expectation of these rewards, but these areas are also activated by abstract rewards such as the promise or depiction of money. Satiety experiments provide a powerful manipulation of an individual’s motivational state, which directly impacts on the reward-value of stimuli. Activity in orbitofrontal cortex (and amygdala) is enhanced by pictures of foods, only when hungry, reflecting the differences in reward. Memory of these food stimuli is also greater when hungry and correlated with amygdala and orbitofrontal activity at the time of presentation. These interventional experiments provide strong evidence for participation of human orbitofrontal cortex and ventral striatum in immediate, prospective and mnemonic processing of rewards.

*Motivational learning*

Trial-by-trial imaging studies of reward-related learning have demonstrated differential involvement of human medial and orbitofrontal cortex in representing rewarding and punishing stimuli, in distinguishing between different degrees of rewards and in re-learning different stimulus-reward associations. The learning of threat and punishment has been explored using fear conditioning. When a stimulus is paired with shock or punishment, learning results. Fear responses are subsequently produced by the previously innocuous stimulus. Enhanced amygdala activity is associated with fear conditioning where a face stimulus (CS+) is paired with an aversive event such as a burst of white noise (US). This may occur independently of conscious awareness and may rapidly habituate once learning is established. Associated increases in insula and anterior...
cingulate activity do not show the same degree of habituation to learned threats, suggesting these regions may selectively mediate attentional and arousal responses to threat

**Attention to, encoding, and recall of emotional material**

Attention is preferentially directed towards emotive stimuli perhaps to facilitate processing and behavioural reactions. Attention and arousal are often correlated and many similar brain regions have been implicated in their control, such as anterior cingulate, parietal and insula cortices. The distracting effect of emotional stimuli (faces associated with threat) on a spatial attention task was examined using fMRI. Predictably, amygdala responses were associated with threat, independent of attention, whereas medial prefrontal, orbitofrontal and parietal cortices were implicated in emotional modulation of attention. ‘Oddballs’ are stimuli that stand out from others by virtue of different characteristic; for example, in a list of words, infrequent rare emotional words are remembered more reliably than non-emotional words in the set (Fig. 3). Amygdala activity is enhanced during encoding of these emotional oddballs. When recalling such emotional word stimuli, there is enhanced activity in prefrontal cortex and hippocampus (areas normally activated to a lesser extent by retrieval of non-emotional episodic memory) and additional activity within amygdala and orbitofrontal cortex, which would have responded to the emotional material at encoding. These two levels of emotional influence on recall suggest dissociable modulatory mechanisms for adaptive enhancement of emotional memories.

**Disorders of emotional learning**

Emotional and social problems are often conceptualized within the framework of re-inforcement-related behaviours, based on observations of deficits consequent to focal brain damage including orbitofrontal cortex and amygdala. Neuroimaging studies continue to provide mechanistic insights into the functional contributions of discrete brain regions to adaptive behaviours. Along these lines, neuroimaging studies have also described microscopic or functional abnormalities in similar regions in patients or offenders with disturbed social and emotional behaviour. The mechanisms explored in studies of fear conditioning and emotional learning have direct implications for understanding the development, maintenance, and potential treatment of emotional disorders such as phobias, post-traumatic stress disorder, and related anxiety disorders. Additionally, differences in brain morphology may underlie
Activity during encoding of emotional material

Left amygdala

Inferior prefrontal cortex

Example stimuli

Fig. 3 There is enhanced memory for emotional information. The figure shows regions active during encoding of emotional ‘oddballs’ from a study by Strange et al. Subjects were scanned reading word lists in which some stimuli ‘stood out’ (i.e. were oddballs) by virtue of being emotionally, semantically or perceptually different. When viewing the emotional words, there was enhanced activity in amygdala and inferior prefrontal cortex. This activity correlated with whether the word was subsequently recalled. The location of amygdala and prefrontal group differences during processing emotional oddballs, relative to control stimuli is shown in the brain sections on the left. The bar charts to the right illustrate that this enhanced activity was associated with emotional, not perceptual or semantic ‘deviance’. Beneath are examples of the stimuli showing emotional (E), perceptual (P) and semantic (S) oddballs.

Individual predisposition to development of anxiety-related disorders\textsuperscript{37,38}. As with OCD\textsuperscript{50}, neuroimaging studies may provide an empirical index of treatment responsiveness in these emotional disorders.

Future developments in neuroimaging studies of emotion

In recent years, two developments have had a great impact on functional imaging studies of emotion: event-related fMRI and subject monitoring.
Event-related fMRI has enabled quantification of trial-by-trial relationship of a stimulus (or response) to evoked regional brain activity, in contrast to blocked fMRI or PET studies. In the context of emotion studies, this has overcome many confounds related to habituation and fluctuating attention and arousal. Subject monitoring during scanning can now be safely achieved at temporal resolutions high enough for combined EEG/fMRI studies, and monitoring changes in autonomic activity have already enabled both on-line indexing of emotional processing and dissociation of arousal-related activity from cognitive aspects of emotional processing. The range of analytical methods available for processing functional imaging data should provide for a more detailed definition of neurophysiological mechanisms underlying emotion; for example, effective connectivity analysis to test for modulatory influences on region-to-region interactions. Nevertheless, interventional studies and the use of patient models provide perhaps the most powerful means of exploring theoretical issues, and the field of functional neuropharmacology remains rather undeveloped with respect to fMRI studies of emotion. MRI advances must be set within the context of other modalities of magnetic resonance imaging. A comprehensive understanding of the neurology of emotion must include detailed structural and neurochemical descriptions. These may be achievable with development and implementation of techniques such as diffusion tensor imaging of axonal tracts, combined with neurochemical information from chemical shift imaging or spectroscopy. These methods, combined with functional data obtained from synchronous fMRI and EEG, remain an obtainable goal for the study of healthy emotional processing and emotional disorders.

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