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2.5.4 The anatomy of human emotion

R. J. Dolan

Introduction

Emotions, uniquely among mental states, are characterized by psychological and somatic referents. The former embody the subjectivity of all psychological states. The latter are evident in objectively measurable stereotyped behavioural patterns of facial expression, comportment, and states of autonomic arousal. These include unique patterns of response associated with discrete emotional states, as for example seen in the primary emotions of fear, anger, or disgust often thought of as emotion proper. Emotional states are also unique among psychological states in exerting global effects on virtually all aspects of cognition including attention, perception, and memory. Emotion also exerts biasing influences on high level cognition including the decision-making processes that guide extended behaviour. An informed neurobiological account of emotion needs to incorporate how these wide ranging effects are mediated.

Although much of what we can infer about emotional processing in the human brain is derived from clinic-pathological correlations, the advent of high resolution, non-invasive functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) has

greatly expanded this knowledge base. This is particularly the case for emotion, as opposed to other areas of cognition, where normative studies have provided a much richer account of the underlying neurobiology than that available on the basis of observations from pathology as in classical neuropsychology.

Emotion has historically been considered to reflect the product of activity within the limbic system of the brain. The general utility of the concept of a limbic-based emotional system is limited by a lack of a consensus as to its precise anatomical extent and boundaries, coupled with knowledge that emotion-related brain activity is, to a considerable degree, configured by behavioural context. What this means is that brain regions engaged by, for example, an emotion of fear associated with seeing a snake can have both distinct and common features with an emotion of fear associated with a fearful recollection. Consequently, within this framework emotional states are not unique to any single brain region but are expressed in widespread patterns of brain activity, including activity within early sensory cortices, shaped by the emotion eliciting context. This perspective emphasizes a global propagation of emotional signals as opposed to a perspective of circumscribed limbic-mediated emotion-related activity.

The amygdala and emotion

The above considerations aside, the structure most closely affiliated with emotional processing is the amygdala. This structure is an anatomically and functionally heterogeneous, bilateral, collection of nuclei located in anterior medial temporal cortex. The importance of the amygdala in emotional control was first highlighted by reports that rhesus monkeys with bilateral temporal lobe ablations no longer show appropriate fear or anger responses.[1] The role of the amygdala in emotion has been subsequently extended by findings that humans with lesions to this structure have impaired emotional recognition, particularly for fear, and no longer acquire Pavlovian conditioned responses[2] (see below). Finally, functional neuroimaging findings show activation of amygdala in responses to face stimuli that depict a range of emotions, particularly fear but also other primary emotions.[3, 4]

The importance of the amygdala in emotion derives in part from its extensive anatomical connections with all sensory processing cortices, as well as hippocampus, basal ganglia, cingulate cortex and the homeostatic regulatory regions of hypothalamus and brain stem.[5] This widespread anatomical connectivity means that this structure can access information processing in multiple brain regions and, in turn, can exert diffuse modulatory influences, including influences on effector autonomic and motor output systems. In this way activation of the amygdala by a sensory based emotional stimulus influences widespread brain regions including those that mediate homeostatic regulatory responses as expressed in altered autonomic state, such as change in heart rate, blood pressure and respiration.

Learning predictive emotional responses

A central role for emotion is to index value, specifically whether present or future sensory events or states of the environment that are likely to be associated with reward or punishment. From this perspective, all emotions are to a greater or lesser degree valanced. For example, an emotion of joy signals a likelihood of reward while an emotion of fear signals a likelihood of punishment. The fact that signals that predict such emotional occurrences are to some degree arbitrary means that the brain must have some means of associating sensory cues with potential emotional outcomes, an ability that seems crucial for adaptive behaviour.

Associative learning provides a phylogenetically highly conserved means to predict future events of value, such as the likelihood of food or danger, on the basis of predictive sensory cues. The amygdala plays a crucial role in mediating this form of emotional learning as evidenced by deficits seen with animal lesion data and learning-related effects seen in human functional neuroimaging experiments.[6, 7] In its simplest form, Pavlovian conditioning is expressed when a previously neutral sensory stimulus (the conditioned stimulus, or CS+) acquires emotional predictive significance through pairing with a biologically salient reinforcer (the unconditioned stimulus, or UCS). With conditioning, the predictive stimulus (CS+) comes to elicit behaviour previously associated with the UCS, but in the absence of UCS presentation. There is a wealth of animal and human data which now shows that the amygdala has a key role in this form of associative learning, for both appetitive and aversive outcomes.

How the brain updates predictions of emotional outcomes

While contingencies acquired on the basis of associative learning provide a basis for generation of predictions of future event of value in response to sensory cues, this form of learning lacks flexibility in optimizing future behaviour. For example, the value of future states associated with predictive cues may change in the absence of subsequent pairing with these cues. Thus, a cue that is associated with a particular food that is valued when a person is hungry has diminished relevance when the person is sated with that same food. Consequently, it is important for optimal adaptive behaviour to be able to maintain an updated representation of the current value of such sensory-predictive cues that does not slavishly depend on new learning in relation to that cue.

Reinforcer devaluation is a standard experimental methodology for examining how value representations accessed by predictive cues are updated. As indicated, in the case of food, its value can be decreased through what is termed sensory-specific satiety. In this type of manipulation, the reward value of a food eaten to satiety is reduced (devalued) relative to foods that are not eaten to satiety. In humans, functional neuroimaging measured brain responses elicited by predictive stimuli (such as a CS+), that have been subject to devaluation, are associated with significant response decrements in the OFC paralleling the behavioural effects of satiation.[8] This response pattern within OFC indicates that this region is involved in representing reward value of predictive stimuli in a flexible manner, observations that also accord with extensive evidence from animal lesion data.[9, 10]

The observation that neural responses evoked by a food predictive conditioned stimulus (a CS+) in OFC are directly modulated by hunger states can inform an understanding of the behavioural impact of pathologies that impact on orbital-frontal cortex, especially the feeding abnormalities observed in both the Kluver-Bucy syndrome and fronto-temporal dementias. Patients with these conditions frequently show increased appetite, indiscriminate eating, food cramming, and change in food preference, hyperorality, and even attempts to eat non-food items. A dysfunctional network

involving OFC and amygdala would mean that food cues, and other predictive cues, are unable to recruit motivationally appropriate representations of food-based reward value.

A computational account of emotional learning

Learning to predict reward or danger is a basic and highly conserved form of learning, as embodied in Pavlovian or associative learning. However, to be maximally adaptive, it is important that this form of learning is used not only to predict but also to shape optimal actions. The computational principles that underpin what is now referred to as value learning, involving prediction and optimization of action with respect to likely future outcomes, is more than an abstract issue and speaks to the critical issue of optimal control in decision-making.

One classical solution as to how associative learning is implemented is by means of a signal, referred to as a prediction error, which registers a difference between a predicted and actual outcome. This type of solution to predictive learning has been formalized within what is known as the Rescorla-Wagner learning rule. Temporal difference learning (TD) provides a more sophisticated computational extension of this learning rule that accounts in a precise manner for how an organism learns to make predictions, as well as select optimal actions, in response to states of the environment so as to maximize long-term reward or avoid long-term punishment.[11] As in the case of the Rescorla-Wagner model, when a positive (or negative outcome) is not predicted there is a large prediction error which reduces to zero when this same outcome is fully predicted. The function of the prediction error is to act as a teaching signal that can both update future predictions as well as shape optimal policies or action choices. In temporal difference learning (TD), credit is assigned by means of the difference between temporally successive predictions, rather than between a predictive stimulus and an outcome, such that learning occurs whenever there is a change in prediction over time.

The importance of the above theoretical considerations rests upon empirical observations that TD error-like responses have now been demonstrated in the response pattern of dopamine neurones recorded in monkeys during associative learning.[12] Consequently, in a classical conditioning context where a stimulus is followed by an unexpected reward it can be shown that dopamine neurones respond with a burst of action potentials after actual reward receipt. Over the course of learning, with repeated presentations of a predictive stimulus and reward, dopamine neurones no longer respond to receipt of the reward. In this latter case, the reward is accurately predicted because of the occurrence of the preceding predictive stimulus. What is now observed is a prediction error at the time of the earliest predictor of this reward, for example at time of presentation of a predictive CS stimulus. Prediction error type brain responses have also been shown to occur in the human striatum and orbital-prefrontal cortex during both Pavlovian and Instrumental learning in humans, as measured by fMRI.[13,14] Indeed, a crucial link between a dopamine prediction error signal, human striate activity and reward-related choice behaviour in humans has also been shown using fMRI techniques. In this latter case, a reward outcome prediction error signal was enhanced by boosting the impact of dopamine using L-dopa (a precursor of dopamine), while a dopaminergic blocker Haloperidol led to an attenuation of a prediction error signal. Crucially, the former manipulation was associated with enhanced reward learning while the latter was associated with impaired reward learning in a manner that indicates that a reward outcome prediction error is involved in shaping optimal behaviour.[15]

How emotion influences memory

The cognitive domain where the modulatory influences of emotion have been best characterized is with respect to episodic memory, the type of memory that underpins autobiographical experience. Emotion enhances episodic memory function as seen in an enhancement for material that encompasses personal autobiographical, picture, and word based-items, an effect best seen in free recall tasks.[16] The critical role played by the amygdala in this modulation is illustrated by functional neuroimaging experiments where amygdala activity during encoding predicts a benefit in later recall of emotional material relative to neutral material.[17] Thus, enhanced amygdala activity at encoding for both positive and negative stimuli is predictive of later episodic memory function, during free recall tasks.

During encoding of emotional items there are bi-directional interactions between amygdala and hippocampus, the latter structure being a region essential for episodic memory formation. The bi-directional interaction between amygdala and hippocampus is inferred from the fact that an enhanced amygdala response, measured using functional neuroimaging, to presentation of emotional items is dependent on influence from hippocampus. Conversely, an enhanced hippocampal response to emotional items is dependent on influences from the amygdala.[18] While these studies were carried out at encoding it is important to acknowledge a role for the amygdala during retrieval of emotional items and contexts.

How emotion influences perception

Emotion often signals an environmental event of value. From an evolutionary perspective, it is important that such occurrences are amenable to privileged perceptual processing. There appears to be two distinct mechanisms by which emotion can influence perception of such event. One of these is through emotion grabbing attention, leading to enhanced deployment of attention to an emotional eliciting stimulus. This would result in preferential detection of emotional events enabling appropriate adaptive responses to be enacted.

There is also evidence for a second means by which emotion can influence perception that appears to operate independent of attention. For example, in visual backward masking paradigms, a target presented for a brief instance can be rendered invisible if it is immediately followed by a second 'masking stimulus'. In situations where the hidden target stimulus is an emotional item, for example, a conditioned angry face or a spider, there is preserved processing. This is evident in differential skin conductance responses (SCRs) to fear-relevant compared to fear-irrelevant unseen targets.[19] Similar findings are reported using what is referred to as an attentional blink paradigm. The latter refers to a situation where detection of an initial target stimulus, in a stimulus stream, leads to impaired awareness, or inattentional blindness, for a successive second target. Critically, when this second target has emotional content there is an increased probability of its detection as opposed to the default attentional blindness.[20]

In terms of anatomical substrates of these modulatory effects, there is compelling evidence to implicate the amygdala. In functional

neuroimaging experiments, using visual backward masking paradigms, an amygdala response discriminates between unseen emotional and unseen non-emotional target.[19] In other experiments that involve overt stimulus presentation, but where attention is systematically manipulated, such that emotional items are presented out of the window of attention, an amygdala response to emotional stimuli is independent of the concurrent attentional focus.[21] Likewise, in studies of patients with either blindsight (loss of primary visual cortex resulting in visual field blindness) or visual extinction (a situation following a lesion to the right inferior parietal cortex whereby subjects cannot consciously represent stimuli in the contra-lesional visual field) demonstrate an amygdala response to emotional stimuli presented out of awareness in the damaged hemifield.[22]

How pre-attentive processing of emotional events influence, and enhance, perception is an important mechanistic question. One possibility is that inputs from emotional processing regions, in particular the amygdala, modulate the very regions involved in object perceptual processing, specifically when this relates to an emotion eliciting object or event. Anatomically, the amygdala receives visual inputs from ventral visual pathways and sends feedback projections to all levels of this pathway. Neuroimaging data provide evidence for enhancement of the strength of connectivity between amygdala and extra-striate visual regions during processing of an emotional visual input. In patients with amygdala lesions, the enhancement of activity seen in early extra-striate visual areas during encoding of emotional items, for example faces, is no longer expressed. Crucially, neuropsychological data from patients with amygdala damage indicate that a perceptual enhancement seen in extra-striate visual cortex for emotional items is abolished following damage to this structure.[23] This type of evidence is consistent with a proposal that boosting of activity in early sensory cortices, when an emotional stimulus is encountered, reflects a direct modulatory influence from the amygdala.

The neurobiology of subjective feeling states

Human emotion research often conflates the neurobiological mechanisms that index the perception or occurrence of an emotional event (representational aspects of emotion) with their subjective experiential counterparts, usually referred to as feeling states. Feelings can be formally defined as mental representations of physiological changes that characterize, and are consequent upon, processing an emotion eliciting object event or image.[24] This definition assigns an important causal role in the genesis of subjective feeling states to afferent feedback to the brain from the body, both sensory and neurochemical. At a broader level, feeling states can be thought of as reflecting the operation of homeostatic mechanisms that underlie survival of the organism. In a recent theoretical model, based on neurological observations, prime emphasis is given to the cerebral representation of bodily states as providing the substrate for the conscious awareness of feeling states.[25]

A key neurobiological question is whether brain systems supporting emotional perception are distinct from those supporting feelings states. Candidate structures that mediate feeling states encompass those involved in bodily homeostasis and that process information regarding the bodies internal milieu including brain stem peri-acqueductal grey (PAG) and parabrachial nuclei, tegmentum, hypothalamus, insula, somatosensory and cingulate cortices. Functional neuroimaging provides strong evidence that feeling states are mediated by distinct neuronal systems to those that support emotional perception.[26] Thus, functional neuroimaging studies of volunteer subjects have shown that the central generation and re-representation of peripheral autonomic states involve structures such as anterior cingulate and insular cortex. For example, recall of subjective feeling states associated with past emotional experiences engages regions encompassing the upper brainstem nuclei, hypothalamus, somatosensory, insular and orbitofrontal cortices. In subjects with pure autonomic failure (PAF), where there is absence of visceral afferent and information regarding the peripheral body state due to selective acquired peripheral autonomic damage, there is attenuation of subjective emotional feelings as well as emotion evoked neuronal activity in regions implicated in mediating feeling states, such as anterior cingulate and insula cortex.[27]

Among the regions most strongly implicated in mediating subjective feeling states is the insula cortex, an extensive region of cortex enfolded from the cortical surface within temporal lobes. Direct evidence for its role in representing subjective feeling states comes from investigations that tap awareness of internal bodily states, such as that required in performing a heartbeat detection task.[28] In this task, subjects who have the ability to detect and accurately report their own heartbeat, which is seen as evidence of somatic awareness, show enhanced activity in the anterior insula cortex when performing such a task.[29]

The proposal that the insula cortex area mediates subjective feeling states is bolstered by evidence that empathetic awareness of the subjective feeling states of others, for example, that engendered when one observes another person receiving pain, is reflected in enhanced activity within anterior insula and cingulated cortex.[30] These same regions are also engaged when a subject is exposed to a pain eliciting stimulus suggesting the same neural matrix that represents subjective feeling states is engaged when representing the subjective feeling states of another person.

(a) Imaging emotional influences on decision-making

Emotion is frequently invoked as influencing decision-making, often detrimentally, a view that tends to pit a hot 'irrational' emotional decision system in opposition to a cold 'rational' cognitive decision-making system. This dichotomy almost certainly represents a simplification and there are compelling neurobiological reasons to suggest multiple decision-making systems in the human brain with emotion in many instances facilitating optimal decision-making.

Real-life decision-making often involves choices between actions which yield potential rewards or punishments, albeit with some element of uncertainty, for example, as manifest in varying probabilities and magnitudes of outcomes. Adaptive decisions that seek to optimize goal-oriented behaviour require an estimation of expected future reward that will follow from choosing a particular action. This behaviour can be described as utility maximization. As outlined previously, reward prediction based on expected reward value can be studied through classical conditioning, in which an arbitrary cue (or conditioned stimulus) takes on predictive value by association with subsequent delivery of an affectively significant or unconditioned stimulus (which can be a reward or punishment, or strictly speaking, an appetitive or aversive stimulus).

Neuroimaging studies implicate OFC alongside structures such as amygdala and ventral striatum in prediction for reward and punishment.[31] As described above, human neuroimaging studies of classical conditioning for reward have highlighted a prediction error signal in prominent target areas of dopamine neurones, including the striatum and OFC. The finding that a neural reward prediction error signal is expressed, present in OFC and striatum, and indeed throughout the reward network, is consistent with the idea that this signal provides a basis for flexible learning and updating of stimulus-reward associations.[33]

Accounts of human decision-making emphasize rationalistic perspectives which invoke analytic processes mediated by an executive prefrontal cortex. An emotional or value based contribution to high level decision-making is evident following ventromedial prefrontal cortex damage where, despite the absence of intellectual deficits, such patients often make real life decisions that are disadvantageous.[33] The types of deficits seen in these patients have been conceptualized as a myopia for the future, in which current needs (as opposed to an integration of current and future needs) dominate decision-making. Observations from patients with this type of lesion has led to the suggestion that this ventromedial OFC provides access to feeling states evoked by past decisions during contemplation of future decisions of a similar nature. Thus, evocation of past feeling states biases the decision-making process, towards or away from a particular behavioural option.[34] However, alternative frameworks that might explain behavioural deficits seen following damage to this region include an inability to represent the value of competing options for action or extreme discounting of future rewards (a myopia for the future), leading to an overvaluing of current as opposed to future rewards.

It is well recognized that normative human decision-making does not always accord with rationalistic perspectives of utility maximization. An influence of prior emotional experience on decision processes is captured by the consequences of an emotion such as regret. Regret is an emotion generated by counter-factual thinking involved in comparing an obtained and foregone outcome which indicates to the subject that the latter, if chosen, would have been more advantageous. In this sense, regret is also a prototypical example of a secondary or higher order emotion, meaning that it emerges out of cognitive or higher order processing as opposed to being stimulus elicited as in the case of fear or disgust (prototypical exemplars of primary emotions). It is known that subjects who experience regret as a consequence of a choice show a subsequent bias away from a rationalistic imperative that invokes a maximization of expected value when making similar choices, an effect that can be explained as regret minimization. This behavioural bias is associated with engagement of the amygdala and orbitofrontal cortices regions, that are also engaged by the actual experience of regret.[35] This pattern of brain response is consistent with theories that suggest evocation of past emotions in the context of decision-making, providing a biasing influence on rational decision processes.

An additional tenet of rational behaviour is the idea that human decisions should be consistent regardless of how choices are presented. One notable deviation from this axiom is described as a framing effect. In simple terms, the framing effect describes a bias in decision-making observed when choices are presented in terms of gain, leading to choices of a sure as opposed to a risky option, versus the same choices presented in a loss where subjects are biased to choose a risky option. Functional neuroimaging data show that a framing engendered bias in human decision-making, risk aversiveness in the gain and risk seeking in the loss frame, is associated with enhanced amygdala activity at the point of decision-making.[36] The suggestion here is that an emotional heuristic, mediated via key emotion processing brain regions, is invoked when humans make decisions under situations where information is incomplete or overly complex.

Conclusions

The neurobiology of human emotion has now undergone a radical revision with the development of sophisticated neuroimaging technologies. There is a clear evidence that it no longer makes sense to think of the brain in terms of simple dichotomies such as limbic and non-limbic. Emotion engages widespread regions of the brain with the precise regions being dynamically con ured as a function of behavioural context. Thus, patterns of brain activity evoked by the seeing a fear eliciting stimulus, such as a snake, are distinct from those evoked when seeing another person in pain. The former situations involve activation of the amygdala and through its modulatory effects it influences widespread interconnected regions, including early sensory cortices. The latter situation results in engagement of distinct structures such as the insula and cingulate cortex. Learning about likely emotional occurrences involves a distinct teaching signal, a prediction error, expressed in widespread brain regions including the striatum and OFC, the latter region mediating a flexible representation of the value of emotional occurrences including reward.

Further information

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2.5.5 Neuropsychological basis of neuropsychiatry

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Introduction

Neuropsychology makes an essential contribution to neuropsychiatry. It seeks objectively to characterize mental competence in component cognitive functions such as perception, attention, spatial cognition, memory, learning, language, thinking, and 'executive' function. Executive function is often associated with the functions of the frontal lobes, although these are not at all synonymous; we will pay special attention to this domain below, as it may be crucial to the understanding of several neuropsychiatric disorders. Neuropsychology is often conveniently divided into clinical neuropsychology and cognitive neuropsychology. The former is primarily concerned with the methodology and psychometric theory that lies behind the selection, administration, and interpretation of standardized psychological tests aimed at assessing deviation from the norm and an individual patient's profile of strengths and weaknesses with a view to optimizing functional outcome and quality of life. Cognitive neuropsychology, by contrast is more concerned with the elucidation of cognitive processes through the study of patients, using both classical and newly devised tasks.[1] Neuropsychology also forms part of cognitive neuroscience, which has as its major goal the understanding of normal, as well as abnormal cognitive function, not only through the neuropsychological study of patients and healthy controls, but also using other techniques, including functional neuroimaging and the use of transcranial magnetic stimulation or psychopharmacology. In practical