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Molecular imaging of the human emotion circuit

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Abstract

Emotions modulate behavioral priorities at the central and peripheral nervous system. Understanding emotions from the perspective of specific neurotransmitter systems is critical, because of the central role of affect in multiple psychopathologies and the role of specific neuroreceptor systems as corresponding drug targets. Here we provide an integrative overview of molecular imaging studies that have targeted the human emotion circuit at the level of specific neuroreceptors and transmitters. We focus specifically on opioid, dopamine and serotonin system given their key role in modulating motivation and emotions, and discuss how they contribute to both healthy and pathological emotions.

Introduction

Emotions prepare us for action. They coordinate systemic activation patterns at multiple physiological and behavioral scales to promote survival. Most modern emotion theories consider emotions as modulatory systems interacting with both lower-order systems such as those involved in homeostasis, as well as higher-order cognitive circuits supporting decision making. Categorical models of emotions propose that evolution has specified a set of basic emotions (usually including anger, fear, disgust, happiness, sadness, and surprise but possibly also others) that support specialized survival functions [1-5]. These basic emotions are characterised by discrete neural and physiological substrates, distinctive subjective feelings (such as “I feel happy”), expressions, and a selective functionally dependent neural basis [6-10]. Much of recent neuroimaging work has aimed at mapping the functional organization of the emotion circuits in the brain using functional magnetic resonance imaging [5,11], and these studies have been successful in delineating the neurobiological architecture of emotions (**Figure 1**).

Meta-analyses of the BOLD-fMRI data have however yielded inconsistent support for the discrete neural basis of emotions. One proposed explanation for this is the low spatial resolution of BOLD-fMRI coupled with univariate analysis: if specific neural populations coding different emotions are intermixed within one voxel, their activation differences cannot be revealed by univariate techniques. In line with this view, multivariate pattern recognition studies have consistently provided support for discrete neural basis of different basic and complex emotions [8,12-14]. Even though multivariate analysis techniques improve the discriminability and specificity of data patterns across different classes or conditions [15], they cannot resolve one of the main limitations of the BOLD-EPI data – that the signal is unspecific with respect to the underlying neurotransmitter circuits.

A single voxel in an echo-planar image may contain neurons operating with a multitude of different neurotransmitters, whose net activation is reflected in the BOLD signal. Understanding emotions from the perspective of specific neurotransmitter systems is however critical, because of the central role of affect in multiple psychopathologies, and the role of specific neuroreceptor systems as drug targets. For example, the most commonly assumed working mechanism of antidepressants involve either increased neurotransmission by increasing synaptic neurotransmitter levels (such as norepinephrine or dopamine (DA)), or specific agonist effects of the targeted receptors. Thus, it is imperative to delineate not just the anatomical but also neuromolecular organization of the emotion circuits in the brain. Here we provide an overview of the molecular mechanisms of emotions, with specific focus on *in vivo* imaging of specific neurotransmitter and neuroreceptor studies in humans. We focus specifically on opioidergic, dopaminergic and serotonergic mechanisms, as they can be readily studied *in vivo* in the human brain (**Figure 2**).

Figure 1. Statistical summary of brain regions involved in emotional processing based on the NeuroSynth database [16].

Studying human neuroreceptor systems *in vivo*

Most commonly used functional imaging (fMRI) and electromagnetic (MEG / EEG) techniques for recording brain activation do not yield any information regarding the underlying mechanisms of neurotransmission. Because pharmacological microstimulation studies are not feasible in humans, main approaches for studying emotion-related neurotransmission involve different activation, blockade and depletion studies, as well as nuclear medicine imaging techniques for direct *in vivo* measurements.

Pharmacological activation and blockage studies

The classical behavioral pharmacological approach involves delivering specific receptor agonists or antagonists or other pharmacologically active agents into the circulatory system, or directly into the target tissue in the case of animal studies. In humans these studies are difficult to conduct, because oral or intravenous administration leads to systemic rather than regionally specific effects, and it has been well established through animal studies that the effects of receptor agonists / antagonists can be regionally highly selective [17]. One way for overcoming this limitation is to use a pharmacological imaging approach, where functional imaging or electromagnetic recordings are performed during pharmacological treatment versus a placebo condition, which allows us to identify the brain regions where drug action leads to neural responses. However, these regional responses may still be influenced by system-level effects, and pinpointing the specific regions whose pharmacological manipulation leads to altered BOLD signal is difficult. Furthermore, these studies employ potent pharmacological agents such as morphine or dexamphetamine that require strict clinical supervision. Finally, pharmacological manipulations may lead to physiological effects that directly confound the BOLD signal, such as respiratory depression caused by opioid agonists [18], further complicating their interpretation.

Monoamine depletion studies

A complementary approach to pharmacological activation and blockage studies involves techniques that temporarily lower the functioning of monoamines such as 5-HT, DA and catecholamine, typically by blocking the synthesis or restricting the intake of amino acid precursors. The three most widely used techniques involve acute tryptophan depletion (ADT) to block 5-HT transporter synthesis by dietary restriction of the 5-HT precursor l-tryptophan. The effect is amplified by consumption of a large quantity of other amino acids that compete with tryptophan at the blood-brain barrier [19]. Phenylalanine/tyrosine depletion (APTD), in turn, targets the dopaminergic / catecholaminic systems by restricting the dietary intake of its precursors phenylalanine and tyrosine. Such techniques result in specific short-term effects in distinct neurotransmitter systems rather than on general protein metabolism in the brain [20], however the interpretation of these results is complicated due to distinct system-level effects on transmitter synthesis. Nevertheless, these techniques are valuable when investigating the involvement of monoamine system function in specific mood disorders.

Molecular imaging with positron emission tomography

Functional molecular imaging using positron emission tomography (PET) is the current gold standard for *in vivo* molecular imaging in humans. It is based on injecting radiolabeled, biologically active molecules into the circulation. These molecules bind to specific target sites, and their unstable isotopes subsequently undergo positron emission decay. The radioisotope emits a positron – an antiparticle of an electron – which loses kinetic energy as it travels through brain tissue. After a certain degree of deceleration, the positron can interact with an electron, leading to an annihilation event producing two gamma photons (rays) moving in opposite directions. The gamma rays are recorded by the detector units of the PET camera, and on the basis of simultaneously detected gamma rays on the opposite sides of the detector ring, the location of the annihilation event can be computed. This subsequently allows reconstruction of the tracer uptake

in the tissue. When combined with measurements of tracer input and output, these raw radioactivity counts can be transformed into biologically meaningful information such as radioligand binding at neuroreceptors.

This technique provides excellent biological resolution due to the potential for developing highly selective radioligands binding to different protein targets, and spatial resolution up to a few millimeters. Despite its high sensitivity for *in vivo* biomarker tracing, PET lacks capability for capturing the underlying tissue morphology; as such, this information usually needs to be acquired through separate MR or CT scans. Functional imaging of slow-acting neurotransmission is however possible [21,22], although temporal resolution is limited to tens of minutes for most neurotransmission studies. Modern integrated PET-MRI -systems [23] also allow for the simultaneous measurement of perfusion with both PET and arterial spin labelled MRI [24,25], or perfusion with MRI and neuroreceptor occupancy (PET) significantly broadening the utility of PET [26]. All in all, the PET technique is currently the most accurate and specific tool available for investigating *in vivo* neurotransmission in humans.

Figure 2. Distribution of type 2 dopamine receptors, μ -opioid receptors and 5-HT 1A transporters measured using PET radioligands.

The dopamine system

Rewards exert a powerful influence on our behavior. Both humans and animals are motivated to obtain various rewards ranging from food and sex to social contact, and the pleasurable sensations we experience on receiving the reward further reinforce our motivation to seek and consume the same reward in the future. The monoamine neurotransmitter dopamine (DA) and its receptors D1-D5 have been well-established as playing a key role in motor control and reward-related behavior and pleasure. There are multiple DA pathways in the brain that consist of neuronal projections which synthesize and release DA (**Figure 3**). The **mesolimbic** pathway projects from the ventral tegmental area (VTA) to the ventral striatum. This pathway is particularly involved in processing incentive salience, generating pleasure responses and reinforcement learning. The **mesocortical** pathway projecting from the VTA to the prefrontal cortex is, in turn, more involved in executive functions although it also contributes to reward processing. The **nigrostriatal** pathway connects substantia nigra to the striatum (putamen and caudate), and contributes critically to motion control. Finally, the **tuberoinfundibular pathway** connects the hypothalamus and the pituitary gland. Importantly, all the main functions of the dopamine system are also central to reward processing, and it comes as no surprise that dopamine system has been implicated as one of the primary molecular pathways for reward [27].

Figure 3. Main dopamine pathways in the brain.

PET studies using the radioligand [^{11}C]raclopride in humans have consistently demonstrated DA release in central pathways during reward processing. Due to the poor temporal accuracy of PET, it is exceedingly difficult to dissect the contribution of reward expectation and consumption phases to the release of DA: It is difficult to design sufficiently long (~45 min) tasks where rewards would be only anticipated but not delivered. As a result, studies conducted in this area mix both anticipation- and consumption-related effects. The PET analysis of DA transmission in reward has shown that feeding – one of the most salient biological rewards – triggers DA release primarily in the striatum. Because the magnitude of DA release is associated with evaluation of the subjective pleasantness of the meal, this finding has been interpreted as evidence for hedonic (rather than homeostatic) responses to feeding [28]. This is further supported by another series of studies, which measured DA release during intravenous glucose / placebo delivery, thus precluding the subjective evaluation of the reward value of the glucose, yet systemically altering the blood glucose levels simulating a postprandial state [29,30]. These studies found no differences between the glucose and placebo conditions, suggesting that alterations in circulating glucose levels are not sufficient for central DA release. Instead, the hedonic responses driven by the orosensory and chemical taste pathways appear to be crucial for the DA response triggered by feeding.

There is less evidence for DA processing of other primary reward signals, but some studies suggest that romantic [31] and maternal attachment-related rewards [32] are processed via the dopamine system in humans. However, these studies are difficult to interpret as the latter [32] reported dopamine activations in regions where [^{11}C]raclopride has either low or no specific binding and no sensitivity to even D2/D3R antagonist challenge [33], and the former was based on an individual-differences approach [31] and failed to show significant main effects of DA release across the whole group of subjects. In addition, murine models typically show a decrease in DA release in response to social contact seeking [34], rather than an increase as suggested by human PET data; this might however be due to cross-species differences. Striatal DA reward signaling has however been shown to extend beyond biologically significant rewards. For example, more “cognitive” rewards such as listening to one’s favorite music [35], gambling [36] and playing video games [37] leads to striatal dopamine release. In all of these tasks the reward value is learned rather than intrinsic, suggesting that acquired reward signals are processed in comparable fashion via DA signaling as those with innate reward value. This is most clearly highlighted by data that shows that simple cognitive tasks such as task switching may trigger striatal DA release as soon as they are coupled with rewards [38].

Negative emotions also induce DA release. One study using [^{18}F]fallypride revealed increased dopamine release in the amygdala and mediolateral frontal cortex during processing of negative

emotional words [39], while a subsequent study using [¹¹C] raclopride found similar effects in the caudate nucleus and putamen [40]. There are multiple possibilities for the apparently contradicting findings showing that both pleasure and displeasure can lead to DA activation. For example, it is possible that the DA response to negative stimuli reflects preparatory avoidance behavior triggered by the aversive stimulus, consistent with the role of DA release in motor responses geared towards specific behavioral patterns. This might be reflected in similar activation as the preparatory approach for rewards during pleasurable events. Finally, type-2 DA receptors (D2R) have also been linked with executive control and working memory [22], and the emotion-dependent DA activations might reflect the prediction and planning of both escape (negative emotions) and seeking and exploration responses (positive emotions).

Recent PET-fMRI fusion imaging has also tried to dissect the specific role of DA in processing different aspects of emotions, specifically the pleasure-displeasure (valence) and arousal axes. This approach is based on separate PET measurement of neuroreceptor distribution, which can then be used to predict emotion-dependent BOLD responses in subsequent fMRI experiments [41]. The logic of these experiments is to examine whether interindividual variation in the regional BOLD responses is dependent on corresponding variability in neurotransmitter availability, which would be indicative of DA involvement in the emotional processes targeted in the fMRI experiment. However, this work has failed to establish associations between D2R availability and emotion-specific BOLD responses [42] and instead suggests a key role of opioid system in modulating basic affective responses (see below).

Given the central role of dopamine in modulating motivation and reward, it is not surprising that dysregulated dopaminergic neurotransmission is the hallmark of numerous addictive disorders [43]. Human imaging studies have demonstrated that alcohol and drug dependence are associated with lowered D2R availability [44-46]. Additionally, drug-induced striatal dopamine responses are blunted in methamphetamine abusers [47]. With behavioral addictions and addiction-like behaviors the results are less clear. Animal studies on obesity suggest that striatal D2R is downregulated in the obese brain [48], while human studies have yielded mixed results with some finding lower [49-51] and others unaltered [29,30,52] D2R availability in the striatum. Finally, pathological gambling is not associated with altered D2R availability [36]. However, gambling-dependent dopamine signalling is amplified in pathological gamblers versus controls [36], in contrast to the blunting effect observed in amphetamine abusers upon drug administration [47]. In sum, substance abuse appears to markedly downregulate the D2R system possibly via direct pharmacological effects, whereas behavioural addictions and addiction-like states are modulated by at least partially independent pathways.

Opioid system

Endogenous opioids are expressed widely throughout the human central nervous system (**Figure 4**) and numerous high-density receptor sites constitute central nodes in the human emotion circuit [53]. Among the three classes of opioid receptors (μ , δ , and κ), the μ receptors mediate the effects of endogenous β -endorphins, endomorphins, enkephalins, and various exogenous opioid agonists [54]. The predominant action of μ -opioids in the central nervous system is inhibitory, but they can also exert excitatory effects. The neurons synthesizing β -endorphin are found in the arcuate nucleus in hypothalamus and the nucleus tractus solitarii of the medulla, which projects extensively to regions throughout the CNS. Dopamine is oftentimes considered as the primary neurotransmitter for reward processing [27]. Opioid and dopamine systems are however closely interlinked on cellular level [55], and opioids can produce reward independently of dopamine [56], likely via partially independent molecular pathways.

Opiates are commonly used illicit drugs particularly in the US, where the lifetime prevalence of opioid use disorder exceeds 2% [57]. Such high misuse potential is attributed to the strong ‘liking’ responses - the pleasurable subjective experiences produced by drug consumption [58]. However, experiments with drug-naïve volunteers have not provided consistent results on opioid agonists associated with liking or pleasure. Some studies report increased pleasure upon μ -receptor (MOR) agonist delivery [59-61], whereas others have not corroborated these findings [62-64]. These discrepancies likely pertain to differences in the route of administration, receptor affinity and genetically determined variation in receptor expression [65]. Some recent experiments have found that opioid agonists shift the evaluation of external stimuli, making them seem more pleasant, without necessarily directly influencing tonic subjective emotional state per se [66]. Thus, it is possible that opioid agonists primarily influence the evaluative processing of emotions, rather than directly modulating the acute subjective feeling. Consequently, opioids might alleviate stress and dysphoria by shifting the evaluation of the internal and external world towards more positive directions.

Figure 4. Organization of the human opioid system in the brain. Note that as specific opioid neuron projections cannot be established, this figure instead characterizes the relative expression of different receptor subtypes in some of the key nodes of the emotion circuit.

By contrast, molecular imaging shows that reward consumption consistently triggers endogenous opioid release. Feeding leads to increased endogenous opioid release in the reward circuit and also elsewhere in the brain [67,68]. However, this response is observed for both palatable and non-palatable meals and is actually stronger for fast-metabolizing, non-appetizing liquid meals than for palatable pizza. Thus, the response is likely a combination of the low-level homeostatic pleasure of feeding after fasting which is presumably more intense in response to a quickly metabolized liquid meal, and possibly a partially independent effect of subjective hedonic responses. Corroborating evidence for the role of the opioid system in processing primary rewards comes from studies showing that pleasurable social interaction [69,70] and strenuous physical exercise [71,72] induce central opioid release. Similarly to dopamine, these effects extend beyond primary rewards, as for example positive moods induced by mere mental imagery induce opioid release in the amygdala [73]. Fusion imaging with PET and fMRI suggests that the opioid system governs particularly the arousal dimension of emotions. The more opioid receptors an individual has in their limbic system, the weaker their arousal-dependent BOLD responses observed in the brain’s emotion circuits [42].

Accordingly, opioid system might act as a buffer against socioemotional stressors, alleviating the negative feelings associated with one's own or another's misfortune [41].

Whereas the general role of dopamine system in drug addictions is fairly clear-cut, the story is more nuanced with the opioid system. Alcohol dependence is associated with elevated MOR levels in the striatum [74,75], whereas cocaine dependence results in similar effects in more widespread regions, particularly cortical and cingulate areas [76]. However, chronic opiate abuse is associated with MOR downregulation [77,78]. Thus, the effects of drug abuse on MOR seem to be drug-specific. More consistent data comes from studies on obesity, that have implicated downregulated μ -receptor action as one of the key pathophysiological mechanisms in the disorder [55,68,79,80]. These effects seem to also be specific to obesity rather than a general feature of behavioral addictions, as μ -receptor downregulation is not observed in pathological gambling for example [81]. Finally, despite the centrality of the opioid system in hedonia and affective functioning, there is no clear evidence of its involvement in the pathophysiology of mood disorders. PET imaging data are limited in scope, and the existing studies have yielded conflicting evidence on opioidergic alterations in major depression [82,83]. However, one recent large-scale study shows that subclinical depressive and anxious symptoms are consistently linked with MOR system downregulation [84]. Finally, opioid system may also contribute to affective pathophysiology due to its role in governing human attachment behaviour whose disruptions are consistently linked with mood disorders [85]. This is supported by PET studies that have consistently found that insecure attachment is linked with downregulated MOR in the limbic and paralimbic regions [86,87].

Serotonergic system

The monoamine neurotransmitter serotonin and its receptors 5HT₁-5HT₇ are involved in the regulation of sleep, appetite, mood and pleasure, but it is also involved in cognitive and physiological processes. In the central nervous system serotonin is produced in the raphe nuclei in the brainstem, from where the serotonergic projections extend to the striatum and neocortex (**Figure 5**). Brain's serotonergic systems also play a critical role in avoidance behaviors as well as fear and anxiety. Activation of the serotonergic system is critical for avoidance behavior in rodents [88], and genetic variations in serotonin transporter (SERT) expression influence the fear circuit's responsiveness to acute threat signals in humans [89]. Thus, major categories of anxiolytic drugs also inhibit SERT.

Figure 5. Main serotonin pathways in the brain.

Whereas dopamine and opioid systems are centrally involved in the pathophysiology of addictive disorders, the SERT system is consistently implicated in mood regulation and consequently in the pathogenesis of mood disorders [90]. Although initial reports on 5-HTT in mood disorders have been variable, meta-analyses suggest that serotonin transporter availability is consistently lowered in depression [91]; but see [92] and altered serotonergic neurotransmission is also considered a hallmark of depression [93]. Accordingly, most widely used and effective antidepressants act by increasing extracellular serotonin levels. Importantly, individual differences in the expression of the serotonin transporter mediate the effects of stressful life events on the onset of depression [94]. In similar fashion, serotonin transporter availability varies seasonally, suggest that altered serotonergic function may also underlie pathophysiology of seasonal affective disorders [95].

Functional molecular imaging of the serotonergic system has been limited due to the lack of radioligands that show sensitivity to endogenous serotonin levels, essentially preventing serotonin activation studies with PET. However, fusion PET-fMRI imaging has elucidated the role of SERT in emotional processing. A number of studies indicate that the serotonergic system regulates amygdala responsiveness to facial expressions of emotions [96-99]. For instance, PET-fMRI studies have found an inverse relationship between 5-HT_{1A} receptor density in the dorsal raphe nucleus (DRN) or HT_{2A} density in the prefrontal cortex and the magnitude of amygdala BOLD response to emotional faces [96-98,100]. Some studies have also yielded conflicting results, with no association between 5-HT_{1A} binding and emotional face processing [101]. For practical and economic reasons, these types of multimodal neuroimaging studies have limited statistical power (oftentimes $n:s < 30$), which may yield inconsistent effects in correlational designs. However, pharmacological activation studies provide corroborating evidence for serotonergic modulation of amygdala responses to threat. Multiple studies have documented that serotonin reuptake inhibitors (SSRIs) modulate amygdala reactivity to emotional facial expressions [102-105]. These effects are however not just face-specific, but extend to emotional processing in general and also to emotions derived from natural speech. The serotonin and norepinephrine receptor antagonist mirtazapine attenuates responses to unpleasant events in sensorimotor and anterior areas while modulating responses to arousing events in cortical midline structures. These effects are paralleled by increased functional connectivity between cortical midline and limbic areas during pleasant events [106], suggesting large-scale modulation of affective processing by serotonergic drugs.

From a clinical viewpoint, subjective feelings linked with the neural and autonomic emotional response are also an important facet of mood disorders. In particular, negative self-concept and increased self-focus play an important role in the pathophysiology of depression. Some studies suggest that the serotonergic system can influence how subjects interpret and process self-relevant affective information. Mirtazapine attenuates self-referential emotional processing in healthy volunteers, as manifested in decreased cortical midline activation [107]. This mechanism could underlie one form of serotonin-dependent antidepressant action. This is further evidenced in clinical trials, which show how short-term escitalopram treatment regulates self-referential processing in patients with major depressive disorder [108]. Thus, serotonergic modulation seems to occur at multiple levels of the human emotion circuit, ranging from sensory to evaluative, cognitive and self-referential processes, and the serotonergic action of antidepressants likely impacts all these levels.

Conclusions

Recent advances in nuclear medicine imaging have helped to elucidate the role of opioid, dopamine, and serotonin systems in human emotions. There is clear evidence that dopamine and opioid systems modulate hedonic processes. However, both dopaminergic and opioidergic activation is observed during negative emotions too, suggesting that they may also support general motivational

and arousal-modulation components of emotions. At a pathophysiological level, the dopamine system is more clearly linked with substance abuse and addictive disorders, whereas opioidergic activations vary from substance to substance, with clear downregulation observed particularly in obesity. The serotonin system links more clearly with negative emotions including fear and sadness, yet outside pharmacological and clinical studies, the majority of these data come from pharmacological fMRI studies and those correlating transporter availability with BOLD-fMRI responses.

There is no clear one-to-one mapping between specific emotions or emotional behaviors and specific neurotransmitters. Obviously numerous neurotransmitters have a wide variety of roles, and their specific actions are not limited to emotional behavior. Human imaging studies are challenging to conduct, and are limited by radioligand pharmacokinetics and affinity. For the major neurotransmitter systems implicated in emotion, reliable radioligands exist for imaging serotonin, dopamine, opioid and endocannabinoid receptors and transmitters. For opioid and dopamine systems, there are also radioligands available that are sensitive to endogenous transmitter levels, whereas this has yet to be achieved for serotonin and endocannabinoid systems. In sum, targeting neurotransmitter mechanisms of emotions using PET is a powerful tool for dissecting the molecular mechanisms of emotions, further potentiated by next-generation PET-MRI devices which allow us to address the molecular specificity of emotion-related BOLD activation.

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