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Prefrontal Regulation of Threat-Elicited Behaviors: A Pathway to Translation

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Abstract

Regions of the prefrontal and cingulate cortices play important roles in the regulation of behaviors elicited by threat. Dissecting out their differential involvement will greatly increase our understanding of the varied etiology of symptoms of anxiety. I review evidence for altered activity within the major divisions of the prefrontal cortex, including orbitofrontal, ventrolateral, dorsolateral, and ventromedial sectors, along with the anterior cingulate cortex in patients with clinical anxiety. This review is integrated with a discussion of current knowledge about the causal role of these different prefrontal and cingulate regions in threat-elicited behaviors from experimental studies in rodents and monkeys. I highlight commonalities and inconsistencies between species and discuss the current state of our translational success in relating findings across species. Finally, I identify key issues that, if addressed, may improve that success in the future.

Erratum >

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INTRODUCTION

Anxiety is a core symptom of a variety of neuropsychiatric disorders, yet our ability to treat it is limited. There has been a dearth of new treatment strategies, despite the ever more sophisticated technology available to image the brains of patients and the advent of viral mediated techniques to dissect brain circuits controlling behavior in animals. Advanced imaging allows for greater visualization of functional and neurochemical activity that should provide insight into the etiology of a disorder. The application of optogenetics and chemogenetics such as designer receptors exclusively activated by designer drugs (DREADDs) in rodents is identifying individual pathways that control threat-elicited behaviors at an ever-finer level of detail. So why haven't these advances led to a therapeutic success story as yet?

A number of factors have hindered progress in translating findings from studies in animals into the clinic. The first is characterization of the disorders. For example, in depression, two patients can be diagnosed with the same disorder but have no overlapping symptoms, suggesting that the etiology varies between individuals and thus so may the treatment. There have been recent calls instead to develop therapies that target specific symptoms, e.g., anxiety, regardless of the disorder, e.g., depression or schizophrenia. While this may be a more fruitful approach, symptoms are themselves poorly characterized and often determined on the basis of a psychiatric consultation or answers to questionnaires. Thus, even if two patients do have the same symptom, it may arise from a variety of distinct psychological/neurobiological causes. For example, as will be described in detail below, anxiety could arise because of uncertainty in the environment or because of difficulty in switching away from salient aversive events. While the outcome in these two situations may be similar, the underlying cause and hence effective treatment may be different. Recognition of this has led to the research domain criteria (RDoC) initiative by the National Institute of Mental Health, which aims to integrate multiple levels of information, from genomics and circuits to behavior and self-report, to create a new taxonomy/characterization of mental health disorders

(Insel et al. 2010). Key to this approach is a fundamental understanding of the neurocognitive processes that regulate behavioral and physiological indices of adaptive emotions in order to understand maladaptive emotions. Animal-based research is necessary to achieve this, since experimental manipulations can establish causal relationships and dissect out the complex interactions between and within neural circuits that underlie both adaptive and maladaptive behavior.

A second factor hindering progress in translation is the lack of focus on the cortical involvement in threat processing in animals. Considerable insight into the core neural circuits underlying threat processing has been gained from studies in rodents. These have dissected out the interaction between the amygdala, hippocampus, bed nucleus of the stria terminalis (BNST), hypothalamus, and more recently the habenula, along with downstream pathways in the brainstem, in the acquisition and expression of physiological and behavioral responses to innate and learned environmental threat (for reviews see LeDoux 2000, Paré et al. 2004, Davis et al. 2010, Krabbe et al. 2018, Tye 2018). In contrast, there is far less understanding of the role of higher-order prefrontal and cingulate regions in the regulation of threat-elicited behaviors generated by this core circuitry, despite the fact that dysregulation in these higher-order cortical regions is commonly reported in clinical imaging studies (see description below). Indeed, LeDoux & Pine (2016) argue that the dearth of new treatment strategies for anxiety and depression is in part due to a failure to differentiate the circuitry involved in defensive responding from that involved in subjective feeling states such as those of anxiety and fear; the latter they hypothesize to be a product of conscious processing in the cortex. The extent to which cortical processing contributes to the subjective feeling state is an issue difficult to assess in animals; nevertheless, considerable insight can be gained from animals by investigating the causal role of cortical dysregulation in fear-like and anxiety-like responses. However, since cortical organization, and in particular prefrontal and cingulate organization, differs considerably between rodents and humans, studies in nonhuman primates (NHPs), in which the organization of these cortical regions is more similar to that found in humans, are essential to bridge this translational gap.

A third factor hindering progress in translation is the reliance in the field on just a few standard laboratory tests to measure fear-like and anxiety-like responses in animals. These tests very often rely on unidimensional response outputs, such as freezing or startle, to a Pavlovian conditioned cue associated with foot shock or time spent avoiding the center of an open field or the open arms of an elevated plus maze (EPM). While these tests have provided considerable insight into the subcortical circuitry underlying threat and anxiety-like responses, as will be discussed below, they may not be sufficient when investigating the higher-order control of such responses.

This review focuses on the prefrontal and cingulate cortex regulation of behaviors elicited by threat and their relevance to the etiology and treatment of symptoms of anxiety. First, I summarize evidence that highlights altered activity within the major divisions of the prefrontal and cingulate cortices in patients with clinical anxiety. I then integrate these findings with our current level of understanding of the causal role of these distinct cortical regions based upon intervention studies in rodents and monkeys. I also highlight commonalities and inconsistencies between and within species in order to assess the current state of our translational success in relating findings across species and to provide insight into how to improve that success in the future.

PREFRONTAL AND ANTERIOR CINGULATE CORTICES IN ANXIETY DISORDERS

Most of our understanding of the neurobiological underpinnings of clinical anxiety has come from neuroimaging. Structural magnetic resonance imaging (MRI), diffusion tensor imaging, task-dependent and resting-state functional MRI, and metabolism studies using positron emission topography (PET) have all been applied to adults with the four major classes of anxiety disorders:

social anxiety disorder (SAD), phobias, posttraumatic stress disorder (PTSD), and generalized anxiety disorder (GAD). Common themes coming out of this extensive literature are changes in gray matter density and in particular altered activity across a network of regions including the amygdala, insula, hippocampus, and of relevance to this review, the anterior cingulate and medial prefrontal cortices. Hyperactivity of the amygdala and insula during task performance, as well as at rest, suggests that these changes may act as a final common pathway across anxiety disorders (Etkin & Wager 2007). Accompanying these changes are reductions in activity in the perigenual anterior cingulate (pgACC), subgenual anterior cingulate (sgACC), and more extensively throughout the ventromedial prefrontal cortex (vmPFC) (for review see Shin & Liberzon 2010), while overactivity is commonly reported in the dorsal anterior cingulate cortex (dACC) and dorsomedial prefrontal cortex (dmPFC). Not every study has reported these changes, however, and some studies have even reported opposite findings. For example, hypo- and hyperactivity have been reported in the sgACC in PTSD, but in this case, the discrepancy may be explained by the more caudal positioning of the hyperactivity within area 25 of the sgACC compared to the more rostrally positioned hypoactivity (Patel et al. 2012). Otherwise, variation has been attributed to disparities between the different classes of anxiety disorders, differences in the comparison control group (e.g., normal unaffected control or unaffected trauma victim for PTSD), the type of trauma experienced (childhood sexual abuse or combat-war exposure), saliency of probing stimuli in functional MRI studies (emotional versus non-emotional), and to whether activity changes are task dependent or seen at rest (Patel et al. 2012).

Increasingly, investigations have focused on functional networks as distinct from independent nodes and have highlighted the altered activity within and between these networks. Menon (2011) introduced the triple framework theory of neuropathology, which included three core networks: default mode network (DMN) (including medial PFC and posterior cingulate cortex, including precuneas), fronto-parietal executive network [including dorsolateral prefrontal cortex (dlPFC) and lateral posterior parietal cortex], and salience network (including the insula and dACC). Altered activity within and between these networks was proposed to underlie cognitive and emotional deficits in a range of different psychiatric, neurological, and developmental disorders. In GAD, for example, the amygdala shows greater connectivity with the executive control network but reduced connectivity with the insula- and cingulate-based salience network (Etkin et al. 2009), whereas in depression, sgACC shows abnormal engagement alongside the DMN (Greicius et al. 2007, Broyd et al. 2009). Disrupted connectivity between networks has also been identified in relation to subdimensions of anxiety, with cognitive anxiety being linked to greater connectivity between the fronto-parietal network and the DMN, and physiological arousal being linked to decreased connectivity between the insula and the medial prefrontal- and orbitofrontal-subcortical networks (Bijsterbosch et al. 2014). The ventral attention network, including the ventrolateral PFC (vlPFC), which is involved in stimulus-driven attention (Sylvester et al. 2012), has also been implicated in anxiety, likely underlying the increased behavioral measures of stimulus-driven attention reported in patients with SAD (Moriya & Tanno 2009) and high-trait (Koster et al. 2006) and state (Pacheco-Unguetti et al. 2010) anxiety.

One important issue to take into account when relating changes in brain activity to psychiatric conditions is which of these changes may be predisposing, in that the individual exhibited functional or structural alterations before the onset of the disorder, and which are acquired, becoming established alongside or after the onset of the disorder. In PTSD, where diagnosis is dependent upon an individual being exposed to a traumatic event, it is possible to sample individuals before or after known adversity. Amygdala hyperactivity in Israeli soldiers (Admon et al. 2009) and reduced pgACC volume in an opportunistic study of earthquake victims (Sekiguchi et al. 2013) appeared to be predisposing factors (seen before stress exposure) for PTSD sufferers,

while acquired abnormalities evident after disease onset included reduced vmPFC-hippocampal connectivity and vmPFC/orbitofrontal cortex (OFC) volume (Admon et al. 2013).

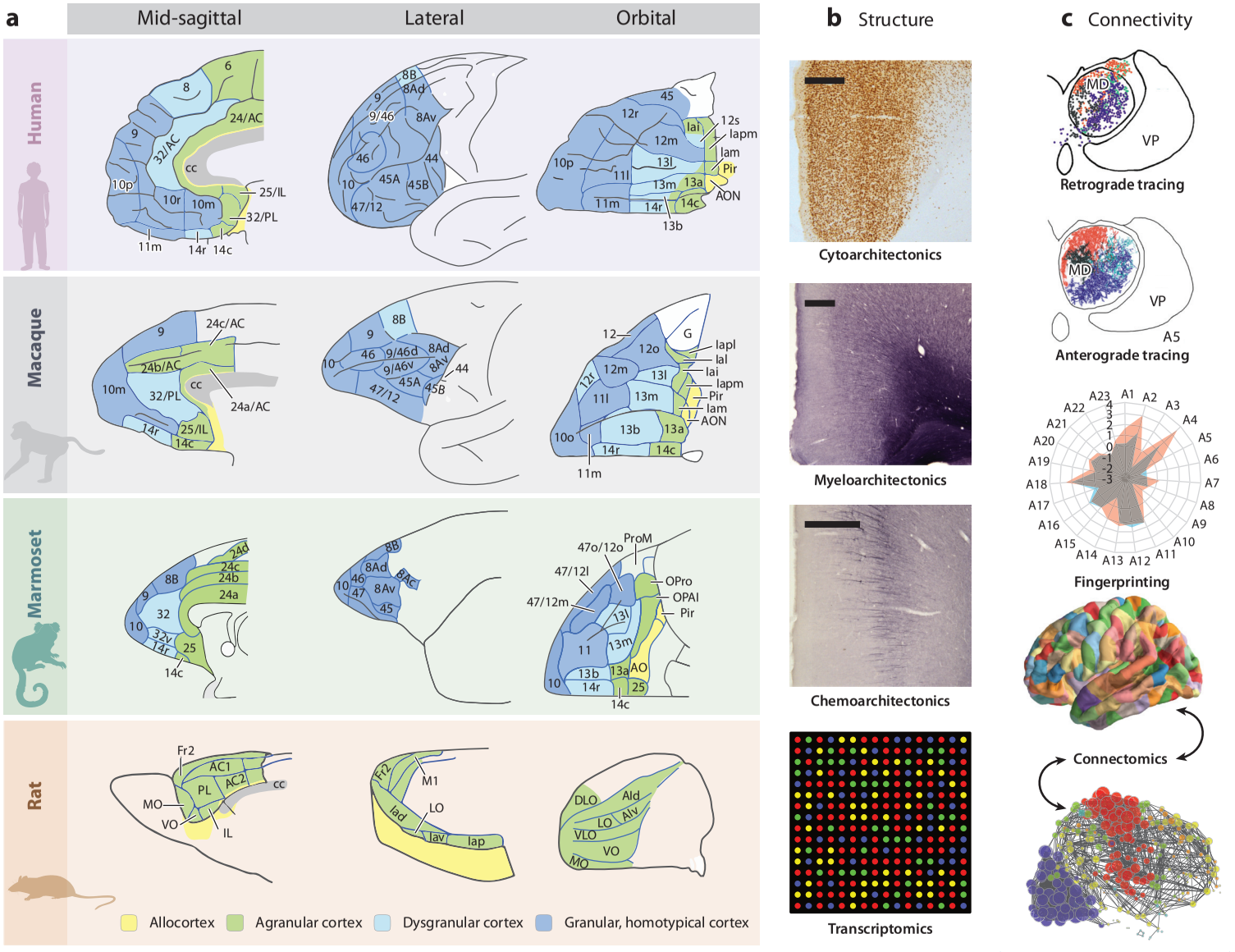
A diagnostic approach has underpinned the majority of studies described so far. However, symptoms of anxiety are not only associated with anxiety disorders but also occur in other neuropsychiatric disorders including depression, and it is not clear whether a dimensional (symptom) approach to studying the neurobiology of anxiety would provide more consistency than a diagnostic approach. These two approaches have been compared recently with respect to the symptoms of anxious arousal, general distress, and anhedonia across the disorders of GAD and major depressive disorder (MDD). Neither a symptom nor a diagnostic approach alone explained the data, which instead were best explained by a combination of the two (Oathes et al. 2015). Anxious arousal was associated with reduced sgACC/ventral striatum connectivity, independent of an MDD diagnosis. On the other hand, general distress (symptom) and GAD (diagnosis) were both associated with limbic-paralimbic (amygdala, hippocampus, ventral striatum, and sgACC) activity, although general distress was the better predictor.

A final consideration is the timing of the onset of anxiety disorders, which very often occurs during adolescence (Kessler et al. 2005). Altered functional activity in the vlPFC is commonly reported in SAD and GAD in adolescents, especially with respect to altered connectivity with the amygdala, although the direction of change and the precise nature of the relationship are task dependent (Monk et al. 2006, 2008; Guyer et al. 2008; Britton et al. 2011; Hu & Dolcos 2017). Structural studies highlight volume reductions in the central OFC in GAD (Strawn et al. 2013) and reduced cortical thickness in vmPFC and hippocampus in a mixed group of adolescents with GAD or SAD (Gold et al. 2017). When adults and adolescents suffering from anxiety disorders have been directly compared, reduced activity in rostral sgACC in response to threat appraisal has been identified as a shared feature, while activity in more anterior vmPFC regions is reduced in adults but heightened in adolescents (Britton et al. 2013).

In summary, marked alterations in activity within and between prefrontal and cingulate networks are found in both adolescents and adults suffering from anxiety, with evidence that alterations within some of these networks may be predisposing. However, many questions are left unanswered: Which of these alterations in activity directly cause the anxiety, and which are compensatory? How do these alterations contribute to the different aspects of anxiety, including negative bias, failure to disengage from salient negative stimuli, and enhanced reactivity to uncertainty? Moreover, how do alterations in activity in one node of a network affect activity in the rest of the network or across networks, and which of these nodes has the greatest impact? It is difficult to address many of these questions without studying the effects of independent manipulations of these brain regions in animals and determining their effect not only on the range of physiological and behavioral responses associated with threat and its regulation but also on activity across brain networks. The following sections review our current knowledge of prefrontal and anterior cingulate regulation of threat responses in rodents and NHPs and assess the extent to which they inform our understanding of anxiety dysregulation in humans.

CROSS-SPECIES HOMOLOGY

The prefrontal and, to a lesser extent, the anterior cingulate cortices of humans and NHPs have expanded considerably compared to similar areas in the rodent (**Figure 1*a***). Thus, particular care must be taken when attempting to directly compare these regions across species so as not to inadvertently confuse rather than clarify. There are many excellent anatomical reviews comparing rodent and primate prefrontal and cingulate cortices (Ongür & Price 2000, Price 2007, Petrides et al. 2012, Vogt & Paxinos 2014); therefore, here I will only highlight some of the core



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Cross-species homology. (*a*) Schematics of the mid-sagittal, lateral, and orbital views of the prefrontal and anterior cingulate cortices in humans, macaques, marmosets, and rats. Specific areas are labeled based on the parcellation maps of Petrides et al. (2012) for lateral views of human and macaque, Ongür & Price (2000) for orbital and medial views of human and macaque, Paxinos (2012) for marmoset, and Palomero-Gallagher & Zilles (2015) for rat. The regions are colored according to whether the cortex is granular cortex (*dark blue*), dysgranular cortex (*pale blue*), agranular cortex (*green*), or allocortex (*yellow*). It should be noted that there are differences in the cytoarchitectonic characterization of granularity in area 8B and area 32 between the parcellation maps of the different primate species. Panel adapted with permission from Wise (2008). (*b*) Structural analyses used to help establish cross-species homologies include cytoarchitectonics (Nissl-stained region of PFC in marmoset), myeloarchitectonics (gold chloride–stained region of PFC in marmoset), chemoarchitectonics (SMI staining of neurofilament protein in a region of dACC in marmosets), and transcriptomics. Black bar = 500 μm. (*c*) Connectivity approaches used to help establish cross-species homologies include retrograde (cholerotoxin) and anterograde (biotin dextran amine) tracing in animals (differential PFC input to and from the mediodorsal thalamus in marmosets) (*red*, medial; *blue*, lateral; *black*, orbital; and *green*, dorsal) (Roberts et al. 2007); fingerprinting, using resting-state connectivity profiles (schematic illustrating imaginary data in which pink and blue represent two different prefrontal regions and their different pattern of projections with brain regions, areas A1–A23) (Mars et al. 2016); and connectomics. Cortical parcellation provided by František Váša and Rafael Romero-Garcia, University of Cambridge, illustrating how connectivity, in principle, can lead to cortical parcellation. Network figure from Nicolas Crossley, University of Cambridge, illustrating how connectivity can reveal different networks (*colored circles*) with each circle representing a different cortical area or node, the size of the circle representing how many connections the area has with other areas, and squares representing hubs, which are nodes with particularly high numbers of connections compared to other nodes. Abbreviations: dACC, dorsal anterior cingulate cortex; MD, mediodorsal thalamus; PFC, prefrontal cortex; VP, ventroposterior nucleus of the thalamus.

issues. Cross-species comparisons can be made at multiple levels of analysis. Structural analysis (**Figure 1*b***) includes cytoarchitecture and myeloarchitecture and neurochemical analysis; it traditionally included neurotransmitters and their receptors but more recently has been extended to gene expression and transcriptomics (Mahfouz et al. 2017). Connectivity patterns (**Figure 1*c***) can be established either by anatomical tract tracing or by neuroimaging (connectomics based on resting-state functional MRI, diffusion MRI, or structural MRI). Functional analysis refers to the fundamental process(es) performed by particular regions, related to specific behaviors and psychological functions.

Structural analysis has identified remarkably similar parcellation of the PFC across humans and NHPs, including Old World macaques (Ongür & Price 2000, Petrides et al. 2012), and new world marmosets (Paxinos 2012), but not rodents, which show a rather distinct organization (Paxinos & Watson 1983, Preuss 1995, Ongür & Price 2000, Palomero-Gallagher & Zilles 2015), although there are common overarching patterns of organization. Comparison is hampered by the lack of consensus in the literature on the terms used to describe rodent PFC (highlighted by Laubach et al. 2018), which often includes areas on the medial wall (variably called medial PFC or anterior cingulate) and the orbital surface. A strong case has been made for similar structural organization of the ACC across humans, monkeys, and rodents, including areas 25, 32, and 24 (Vogt et al. 2013, Vogt & Paxinos 2014) that, based on the fourth edition of the atlas *The Rat Brain in Stereotaxic Coordinates* by Paxinos & Watson (1998), roughly correspond, respectively, to infralimbic cortex (IL), prelimbic cortex (PL), and Cg1/Cg2. However, this parcellation has been revised in the seventh edition of that volume (Paxinos & Watson 2013), and for example, the rostral part of PL has been renamed area 32 while the caudal part of PL and Cg1/Cg2 have become subregions of area 24. The similarity of structural organization between orbital areas between humans/NHPs and rodents is less clear because of the granular/dysgranular subregions in humans/NHPs that are lacking in rodents (Wise 2008).

Anatomical connectivity, as determined by anterograde and retrograde tract tracing, reveals commonalities but also differences in connectivity patterns between OFC and ACC in NHPs and rodents, but an in-depth comparison for many regions is lacking. For example, it is unclear how the connectivity patterns of different areas of primate and rat OFC map onto one another, although Haber and colleagues (Heilbronner et al. 2016) suggest some similarities between

medial/central regions of macaque OFC and medial (MO) and lateral-ventral (LO-VO) regions in rat OFC based on striatal efferents (cf. Ongür & Price 2000 for alternative viewpoint). Area 25/IL appears most similar across macaque and rat (reviewed in Alexander et al. 2019a), while PL in the rat has similarities with both primate areas 32 and 24, and there are differences and similarities in connectivity between rodent areas Cg1/Cg2 and primate area 24 (Heilbronner et al. 2016). This highlights the need for a more comprehensive, brain-wide comparison and to create fingerprints of the connectivity patterns of each region. Such large-scale tract-tracing studies, for example, are currently underway in the marmoset in Japan (**http://riken.marmoset.braincircuits.org**) and Australia (**http://marmoset.braincircuits.org/**).

Neuroimaging lends itself more easily to large-scale mapping, and resting-state functional MRI has been used to identify, for example, those areas in humans that are most similar to functionally distinct regions in the sgACC of macaques and vice versa (Neubert et al. 2015). This hypothesis-driven and region-selective approach contrasts with exploratory approaches that use graph theory to derive connectomes (for review, see van den Heuvel et al. 2016), which have been used to compare the overall organization of the neocortex across species (Li et al. 2013). More recently, multimodal imaging data sets with a range of morphometric variables (e.g., cortical thickness, sulcal depth, myelination) have been used for cortical parcellation (Van Essen & Glasser 2018) and to allow the construction of individual structural connectomes in humans and macaques (Seidlitz et al. 2018).

The similarity of connectivity between brain regions across species should ultimately reflect the extent to which regions share functional homology, but this cannot be determined without parallel studies directly comparing the functions of prefrontal and cingulate regions. However, such studies have again led to differing claims of comparability between different brain regions. For instance, the medial PFC in rodents (an area variably including PL, IL, and sometimes Cg1/Cg2) has been likened to primate dlPFC or vlPFC because of its involvement, respectively, in tests of working memory and attentional set-shifting (Rich & Shapiro 2007, Hernandez et al. 2018). However, rodent PL, in particular, has also been likened to primate dACC (area 24) (Milad et al. 2007a) based on studies of conditioned threat and to vmPFC (Balleine & O'Doherty 2010) based on studies of instrumental contingency and action control. All these comparisons can be contrasted with evidence from cytoarchitectonics, already described above, which identifies this same region as area 32 (Vogt & Paxinos 2014). This raises the question as to just how functionally homologous regions of rodent, monkey, and human PFC/ACC will turn out to be. Using similar, if not identical, behavioral tests across species is thought to facilitate cross-species comparisons, but even when the exact same test is used, different species may apply different strategies to achieve the same goal, so seemingly similar impairments caused by lesions of a brain area across species may not necessarily reflect functional homology between those brain areas. This theme will be returned to in the discussion of the evidence for the roles of different regions of PFC and ACC in the regulation of threat-elicited responses.

INVESTIGATIONS INTO THE INVOLVEMENT OF MEDIAL PREFRONTAL/ANTERIOR CINGULATE AND ORBITOFRONTAL CORTICES IN THREAT PROCESSING IN RODENTS

Behavioral Tests Used to Study Threat Processing in Rodents

A variety of tests have been employed to study the prefrontal regulation of threat processing in rodents, only some of which have been effectively translated into studies in humans. Pavlovian conditioning, and in particular Pavlovian extinction, is one such successfully translated test. In it, a previously neutral stimulus, such as a tone or light, is paired with an unconditioned aversive

stimulus (US), such as foot shock in rodents or aversive loud noise or wrist shock in humans, and the subjects develop conditioned threat responses to the conditioned stimulus (CS) in anticipation of the US. Subsequent presentation of the CS in the absence of the US measures how well a subject can successfully extinguish (regulate) the conditioned threat response once the threat has been removed. Failure or slowed ability to extinguish is a marker of impaired regulation and is argued to be highly relevant to those disorders such as PTSD, phobias, and panic disorder in which threat responses appear unregulated (Milad et al. 2006, Admon et al. 2013). Early studies in rodents measured multiple physiological and behavioral responses, including blood pressure (BP), heart rate, and behavioral freezing (Iwata & LeDoux 1988). Interestingly, these measures differentiated between associative and non-associative conditioning, such that increased BP and freezing were only associated with a CS specifically paired with foot shock, while heart rate increases were associated with both paired and unpaired CSs. Moreover, only the autonomic control of heart rate in the associative condition was a consequence of coactivation of both parasympathetic and sympathetic divisions, while the non-associative condition was the result of sympathetic activation only. This illustrates the richness of information obtained by studying these multiple outputs, especially since marked alterations in cardiovascular reactivity and reductions in parasympathetic control are characteristic of anxiety disorders (Lang et al. 2016, Makovac et al. 2016, Paniccia et al. 2017). Despite this, freezing has since become the most popular single independent measure in rodents, while autonomic measures, including skin conductance and heart rate, are most commonly used in humans (Phelps et al. 2004). Thus, unfortunately, although the same test is applied across species to aid translation, the measuring of different outputs may hinder comparison, especially since it has been shown in marmoset monkeys (see below) that these outputs can become uncoupled after brain manipulations (Reekie et al. 2008). Also hindering comparison are the marked variations in the parameters used when administering Pavlovian conditioning within or between species, which can have a marked influence on the psychological processes engaged (Sharpe & Killcross 2018) and which is discussed in more detail below. Other behavioral paradigms focus on avoidance rather than freezing, whereby the animal either learns to shuttle backward and forward between the sides of a shuttle box to avoid unsignaled foot shock (Moscarello & LeDoux 2013) or climbs onto a safe platform during a CS that signals an upcoming US (Bravo-Rivera et al. 2014). Also successively used in both rodents and humans is the fear-potentiated startle test, which measures the effectiveness of a Pavlovian conditioned threat cue in potentiating an elicited startle reflex (Brown et al. 1951, Grillon & Davis 1997).

Tests hypothesized to be more relevant to disorders such as generalized anxiety are those in which the threat is less certain or more ambiguous. Fear-potentiated startle has been adapted in both rodents and humans so that the threat of an aversive stimulus, e.g., a shock, is unpredictable, occurring randomly within a lengthy cue period or outside of a cue period (Davis et al. 2010, Robinson et al. 2012). Here, the anxiety has been likened to sustained threat, as threat is present but unpredictable. These conditions have not, however, been tested in the context of rodent PFC/ACC function. Other tests of uncertainty in which prefrontal manipulations have been tested rely on rodents' innate avoidance of open spaces and aversion to novel environments such as open field, EPM, and novelty-suppressed feeding (Rodgers & Dalvi 1997, Prut & Belzung 2003). These tests measure the animal's response to potential threat but have not so easily been translated into studies in humans and can also have the drawback that behavior is dependent upon a number of uncontrolled factors, including individual variation in responsivity to such environments and in the drive/need to explore and find food/mate, etc., which make the interpretation of results difficult. However, building on the ethological validity of such tests, explicit foraging tests have been developed in both humans and rodents that facilitate the study of the distinct stages of information processing when encountering threat, from the pre-encounter stage, when

there is risk in the absence of immediate danger, to the post-encounter stage, when a predator is detected, to the circa-strike stage, when there is proximal or distal interaction with a predator. Rodents are given the opportunity to forage for food in a semi-natural environment in the face of either the threat of unpredictable foot shocks or a programmed predator-like robot. In contrast, computerized tests in humans involve subjects foraging but having to avoid a virtual predator that can chase, capture, and cause varying levels of pain (for review, see Mobbs & Kim 2015). Unfortunately, the latter tests have not yet been applied to the study of PFC/ACC in animals.

Medial Prefrontal/Anterior Cingulate Cortices

Areas included within these regions are IL, PL, Cg1, and Cg2. They are interchangeably called medial prefrontal and anterior cingulate cortex (see Laubach et al. 2018 for a recent discussion on this variable terminology). It has been PL and IL, however, that have received the most attention with respect to the regulation of responses to explicit or uncertain threat.

Conditioned threat. Using a simple, single CS Pavlovian conditioning task, many studies have implicated IL in the extinction of conditioned threat responses, and in particular in their recall, while PL has been implicated in the expression of conditioned threat responses (for reviews, see Milad & Quirk 2012, Giustino & Maren 2015). Where studies have interrogated the involvement of Cg1/Cg2 to threat conditioning, the effects appear confined to acquisition rather than expression, with pretraining lesions or inactivation impairing the acquisition of cue-dependent conditioned freezing (Bissière et al. 2008). Conversely, pretraining activation facilitates acquisition and interferes with extinction (Bissière et al. 2008). NMDA receptor antagonists block the formation of conditioned contextual freezing (Zhao et al. 2005), while excitatory amino acids induce avoidance learning without noxious stimuli (Johansen & Fields 2004). In addition, Cav1.2 type 1 Ca^{2+} channel deletion specifically within Cg1/Cg2 disrupts observational threat conditioning, whereby animals develop freezing responses through social observation (Jeon et al. 2010).

Uncertain threat. Involvement of medial prefrontal/anterior cingulate regions in innate behavioral responses to uncertain threat as measured in the EPM and open field has been less consistent. Initial studies that did not explicitly target specific medial PFC subregions reported reductions in avoidance of open arms in EPM following excitotoxic lesions (Shah & Treit 2003). Subsequently, early studies of selective targeting of the PL used methods such as permanent electrolytic lesions (Jinks & McGregor 1997) or temporary inactivations with TTX (Corcoran & Quirk 2007) that likely impacted on fibers of passage, and the results were inconsistent. However, selective inactivation of PL with the GABA receptor agonist muscimol (Sierra-Mercado et al. 2010) or with a sodium channel inhibitor (Stevenson 2011) had no effect on the open-field test, while activity in PL did contribute to an anxiety-like response in the EPM (Stern et al. 2010). Inconsistencies are also apparent following selective IL manipulations. Activation is reported to enhance (Bi et al. 2013), reduce (Gasull-Camós et al. 2017), or have no effect (Suzuki et al. 2016) on anxiety-like behavior in tests including EPM, open field, and novelty-suppressed feeding. Similarly, involvement of Cg1/Cg2 is unclear, with excitotoxic lesions reported to have no effect on EPM (Bissière et al. 2006), inactivation reported to reduce anxiety-like behavior on EPM (Kim et al. 2011), and repeated stimulation found to enhance novelty-suppressed feeding (Barthas et al. 2015). There are many reasons for these mixed effects, including species differences (mice versus rats), the precise neurobiological impact of the pharmacological intervention, habituation experience (or not) to another test environment before the open-field test (e.g., Bi et al. 2013 versus Suzuki et al. 2016), and whether performance was tested in the animal's subjective night (Bi et al. 2013, Suzuki et al.

2016, Gasull-Camós et al. 2017) or subjective day (Adhikari et al. 2015). Testing in subjective night in particular could have a major impact on the levels of stress experienced by the animal during the test and thus influence the results of intervention studies in an area, such as IL, which is highly sensitive to the deleterious effects of stress (see discussion below).

More recent studies have highlighted differences between the effects of global inactivation or activation of a cortical region as compared to pathway-specific effects. For example, selective activation of the IL projections to the amygdala in mice, using optogenetics, decreases avoidance of open arms on the EPM and reduces the normal increase in respiration rate in an open field, whereas such effects are absent when directly exciting IL globally (Adhikari et al. 2015). Correspondingly, inactivation of the same IL-amygdala pathway increased avoidance of open arms in EPM but inactivation of IL globally did not.

In summary, as illustrated in **Figure 2*a***, the opposing effects, respectively, of PL and IL inactivation on the expression of conditioned freezing and recall of the extinction of conditioned

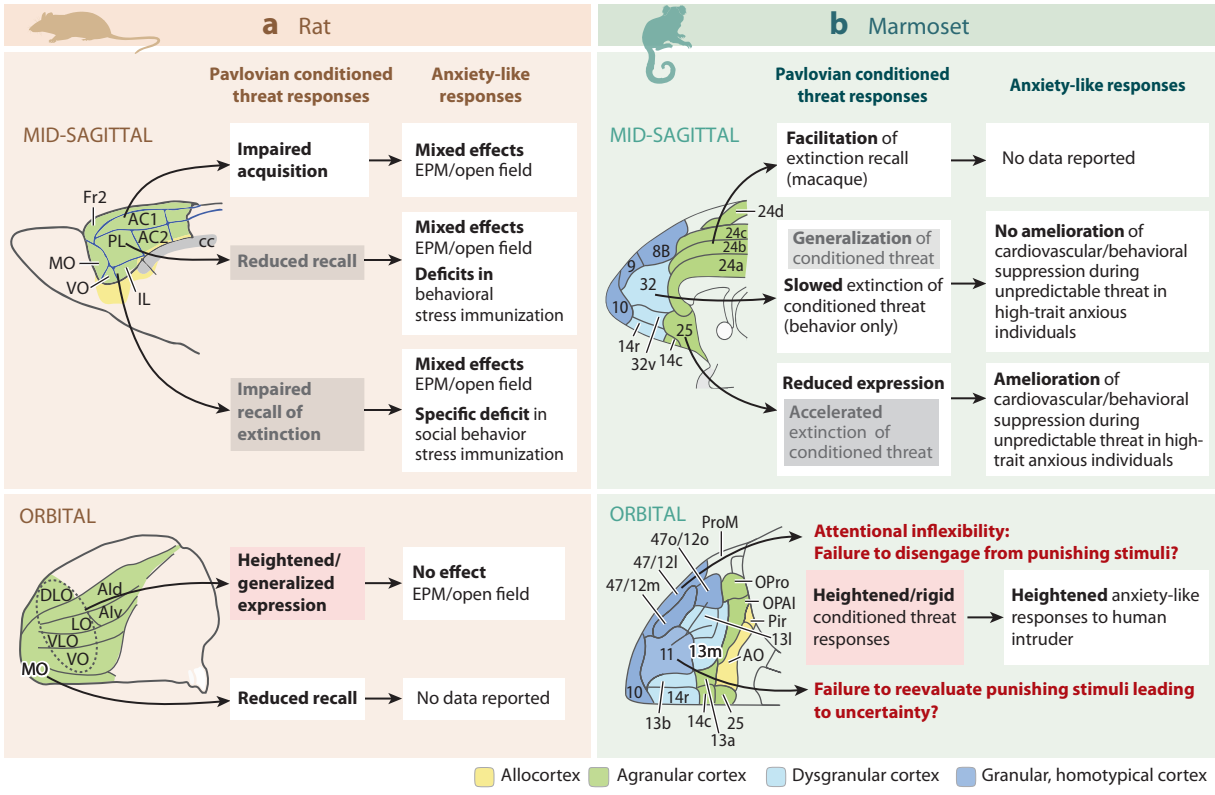


Figure 2

Comparison of the effects of permanent or temporary inactivations of distinct regions of the PFC and ACC in rodents and monkeys on Pavlovian conditioned threat responses and anxiety-like responses. (*a*) Effects of inactivations in AC1/AC2 (Cg1/Cg2), PL, IL, OFC (including DLO, LO, VLO, VO), and MO of rodents. (*b*) Effects of inactivations of area 24 in macaques and areas 32, 25, 11, and 47 in marmosets. A pink background indicates that inactivations of a putative comparable region across species produce a similar effect, i.e., heightened/generalized conditioned threat following OFC inactivations. A gray background indicates that inactivations of putative comparable regions across species produce opposing effects (i.e., rodent PL versus marmoset area 32, rodent IL versus marmoset area 25). Abbreviations: ACC, anterior cingulate cortex; DLO, dorsolateral orbitofrontal cortex; EPM, elevated plus maze; IL, infralimbic cortex; LO, lateral orbitofrontal cortex; MO, medial orbitofrontal cortex; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PL, prelimbic cortex; VLO, ventrolateral orbitofrontal cortex; VO, ventral orbitofrontal cortex. Rodent medial PFC map adapted with permission from Wise (2008).

freezing appear relatively robust, although there are exceptions to their hypothesized opponency, reviewed by Giustino & Maren (2015) and discussed below with respect to stress controllability. Cg1/Cg2, on the other hand, appear more involved in the acquisition of conditioned responses. In contrast, there is little evidence for the involvement of the PL in regulating innate anxiety-like responses in the EPM and open field, while there may be a contribution from Cg1/Cg2. IL may also be involved, particularly when focusing on specific IL outputs to the amygdala.

Stress and its control. The involvement of both IL and PL in the regulation of behavioral responses to stress is clearly seen in the behavioral immunization effect of learned control over a stressor. Animals exposed to uncontrollable tail shocks show prolonged release of serotonin from the dorsal raphe serotonin neurons, and subsequently they fail to learn an escape response in the shuttle box and show heightened contextual threat conditioning, reduced extinction, and reduced social interaction—a pattern of effects known as learned helplessness (Seligman 1974, Seligman & Beagley 1975). In contrast, animals that learn to escape tail shock by running in a wheel show a truncated rise in serotonin release and an immunization effect, so that subsequently they learn to avoid shock more effectively in the shuttle box and display reduced contextual conditioned freezing, more rapid extinction, and increased social interactions (Maier 2015). The immunization effect appears particularly dependent upon the PL, since inactivation of the PL disrupts behavioral immunization across the range of contexts, whereas the effects of IL inactivation appear more restricted to social behavior (Christianson et al. 2014). Moreover, only neurons in the PL (but not IL) projecting to the dorsal raphe nucleus show selective activation to escapable stress (Baratta et al. 2009) and thus are in a position to inhibit serotonin release. The involvement of the PL in mediating the immunization effects of controllability on responsivity to threat, however, seems somewhat at odds with its proposed role in maintaining conditioned freezing. Instead, it points to a more complex role for the PL in the regulation of threat processing, a theme returned to below when considering issues of functional homology.

While the role of the IL in the behavioral immunization effect remains less clear, the sensitivity of the IL to stress per se is very consistent. Chronic stress can induce morphological changes within PL and IL (Wellman & Moench 2018), but the IL is also sensitive to acute episodes of stress, showing apical dendritic retraction and reduced spine-induced learning (Izquierdo et al. 2006, Moench et al. 2016). In both cases, recall of extinction of conditioned freezing is also impaired. Moreover, the serotonin innervation of the IL, but not PL, is increased following intermittent stress during early adolescence, and this is accompanied by the emergence of an anxious phenotype in adulthood, although whether these structural and behavioral phenotypes are related has not been investigated (Moench et al. 2016). If corticosterone levels are elevated chronically via an implant in either PL or IL for seven days, there is increased avoidance of open arms in the EPM (Croteau et al. 2017), suggesting that anxiety-like behavior can be affected by alterations of activity in these regions in certain contexts.

Orbitofrontal Cortex

The OFC of rodents is composed of a number of cytoarchitectonically distinct subregions, but unlike the ACC, where cyto-, myelo- and chemoarchitectonics do support structural homology between rodents and primates, rodent and primate OFC does not display such an evident homology. Because of the lack of a granular layer IV, it has been proposed that these regions are most similar to the agranular regions of the posterior OFC in primates (Wise 2008). Alternatively, a slightly revised proposal based on connectivity patterns (Price 2007) suggests that rodent medial orbital (MO) and ventral orbital (VO) regions may be comparable to primate area 14, rodent

ventrolateral orbital (VLO) and lateral orbital (LO) regions to primate area 13, and rodent dorsolateral orbital (DLO) region to the orbital sector of primate areas 12 and 47.

Conditioned threat. There have been far fewer studies focusing on the role of OFC, compared to medial PFC, in conditioned threat, and those studies that have explored the topic reveal varying contributions of the distinct OFC regions. Those papers in which the effects of the manipulation cannot be explained by damage to fibers of passage have shown mixed effects both within and across OFC subregions on Pavlovian conditioning tasks (for review, see Shiba et al. 2016). The tasks have varied, ranging from acquisition and expression of single and discriminative cued and contextual conditioning to extinction recall. However, in general, when effects following temporary or permanent loss of function are seen, it is to heighten or cause generalization of an animal's threat responsiveness (**Figure 2*a***), regardless of whether the interventions are excitotoxic lesions of agranular insula (AI)/DLO, LO (Lacroix et al. 2000, Zelinski et al. 2010), DLO (Ray et al. 2018), or LO-VO (Costanzi et al. 2014), or inactivation of LO (Sarlitto et al. 2018). Moreover, inactivation of LO using CaMKII-driven inhibitory Gi-coupled DREADD disrupted extinction recall when activated by CNO (DREADD activator) during the extinction phase (Zimmermann et al. 2018). In contrast, in the one study in which MO was temporarily inactivated during recall of conditioning in the absence of the US, reduced recall of conditioned freezing was apparent at the start of the session (Rodriguez-Romaguera et al. 2015).

Uncertain threat. Very few studies have investigated the effects of OFC manipulations on avoidance of mild, potentially threatening unconditioned stimuli or contexts, as tested with the EPM and open field. However, in those that have, it appears that the anxiety-like behaviors normally elicited are unaffected in OFC-lesioned rats with excitotoxic lesions targeting either LO and AI/DLO (Lacroix et al. 2000) or primarily LO and VO (Rudebeck et al. 2007, Orsini et al. 2015); however, the latter manipulation did reduce the time taken to begin eating in a mildly anxiogenic environment (Rudebeck et al. 2007). On the other hand, infusions of an atypical cannabinoid receptor agonist into MO reduces acute stress-induced anxiety-like behavior in EPM and open field (Shi et al. 2017).

PREFRONTAL AND CINGULATE STUDIES OF THREAT PROCESSING IN MONKEYS

Behavioral Tests Used to Study Threat Processing in Monkeys

In the past, a somewhat different set of tests has been used to study negative processing in monkeys compared to rodents and adult humans. This has made it difficult to translate findings either forward into the clinic or backward into rodents, in which there is already a wealth of understanding of the subcortical threat circuits. Traditionally, primate studies have measured innate fear-like behavioral responses to stimuli such as snakes or anxiety-like responses to ambiguous stimuli such as unknown humans. The latter responses are more akin to the anxiety-related innate responses measured in the open field and EPM tests used in rodents. However, the extent to which previously learned experiences contribute to an animal's response in these ambiguous contexts is unclear, and certainly in the case of the unknown human test in monkeys, it may be variable due to the past experiences that individual monkeys have had with humans. In contrast to the majority of neurobiological studies using open field and EPM in rodents (but see Roseboom et al. 2007, Adhikari et al. 2015), it has been traditional to measure multiple behaviors and physiological responses in monkeys in response to snakes and human intruders. This provides for a much richer analysis

of their reactivity (Shackman et al. 2013, Shiba et al. 2016) and greater insight into the differential role of the structures within the underlying neural network (Shackman et al. 2013). Often the individual measures have been combined to create an overall anxiety-like score. Although a comparable test to the human intruder is not used in adult humans, a similar test used in infants identifies those children with an extreme anxious temperament who are most likely to go on and develop stress-related psychopathology later in life. This has led to a highly translatable program of research in macaque monkeys studying the genetics, heritability, and neuronal networks that may underlie such vulnerability (for review, see Kalin 2017).

To aid translatability, researchers have developed Pavlovian threat conditioning and fear-potentiated startle paradigms for primates, similar to those used in both rodents and humans. Rather than using foot shock, most commonly employed in rodent studies, such studies have used aversive loud noise (Mikheenko et al. 2015) or a rubber snake (Wallis et al. 2017) as the unconditioned threatening stimulus in marmosets or an air puff in macaques (Antoniadis et al. 2007, Klavir et al. 2012). Since the measure of an emotional/threat-related Pavlovian conditioned response in experimental studies in humans is very often autonomic reactivity, rather than any behavioral response (Phelps et al. 2004, Kalisch et al. 2006), cardiovascular responses (BP, heart rate, heart rate variability) are often measured alongside behavior (vigilant scanning), thereby providing a richer measure of the threat response. The importance of multiple measures in Pavlovian conditioning is exemplified by a study in which excitotoxic lesions of the anterior OFC in marmosets not only disrupted the ability of the marmoset to track changes in the reward contingencies between an auditory CS and access to a box full of marshmallows, but they also caused an uncoupling of the behavioral output from the cardiovascular outputs (Reekie et al. 2008). We argued that the resulting ambiguous peripheral feedback that such uncoupling creates may have a marked impact on emotion regulation and experience. Indeed, such disjunctions have been reported in schizophrenia patients (Williams et al. 2007) and a subset of children with autism (Hirstein et al. 2001) and are hypothesized to contribute to symptoms of paranoia and stereotypy, respectively. Thus, a more comprehensive analysis including multiple outputs can provide a much deeper insight into the effects of brain manipulations in animals and can strengthen the translation of findings to the human condition and, importantly, into the clinic.

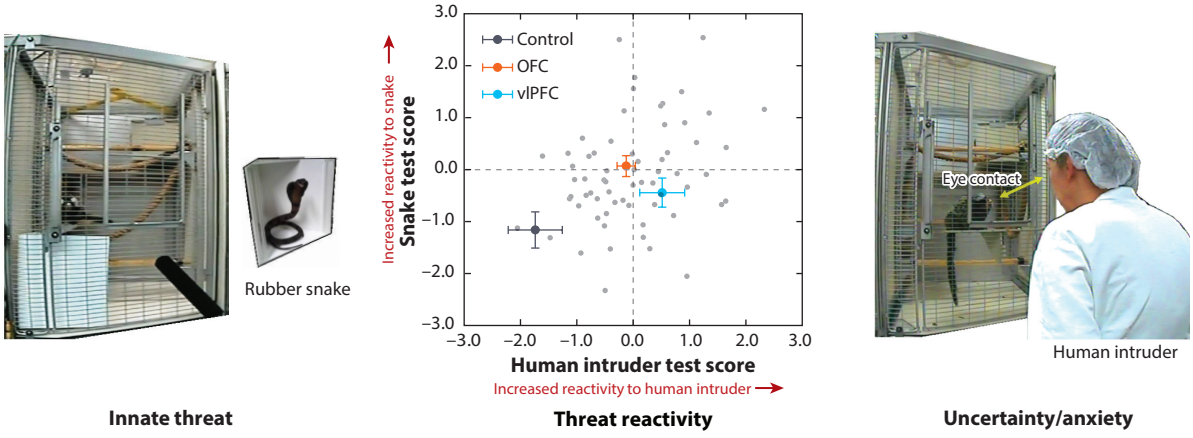
Ventral Prefrontal Cortex

Early primate studies of negative processing focused primarily on ventral regions of the PFC, such as orbitofrontal and ventrolateral areas. They generally reported reductions in reactivity to both innate and ambiguous stimuli following varying degrees of damage to OFC and vlPFC of Old World monkeys (reviewed in Shiba et al. 2016). These early studies did not explicitly investigate the effects of lesions to regions of the medial PFC/ACC, although some of the orbitofrontal lesions did extend onto the medial surface. However, these large lesions were created using the ablative method, which has been shown to disrupt fibers of passage, thereby also disconnecting regions of the PFC outside the target area of ablation (reviewed in Rudebeck & Murray 2014). When excitotoxic lesions targeting intrinsic cell bodies were performed in an extensive orbitofrontal area including areas 11, 13, and 14, the normal ablation-induced blunting of reactivity to a rubber snake, as measured by time taken to retrieve food reward, was no longer observed (Rudebeck et al. 2013). Thus, the overall blunting of negative affect may have been a consequence of widespread disconnection of the ventral and medial PFC from subcortical networks.

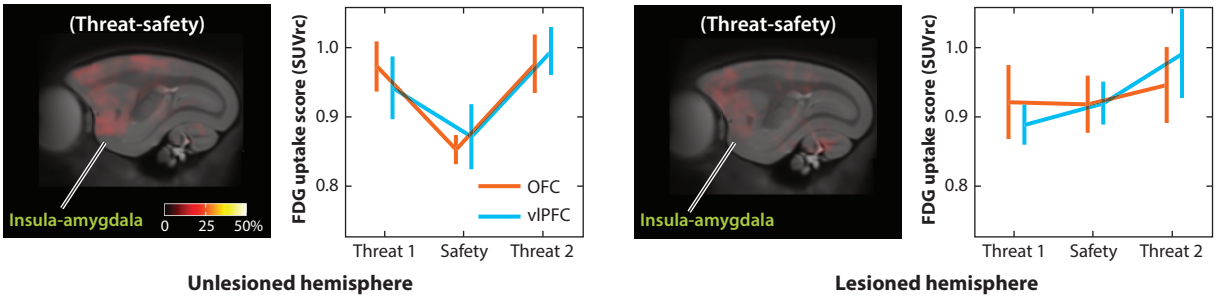
More recent studies in which excitotoxic lesions have targeted more discrete regions of the OFC (primarily area 11) and vlPFC (area 47) have found marked changes in threat reactivity. However, increased reactivity, rather than blunting, was seen in marmoset monkeys using tests of innate threat and anxiety that were relatively similar to those used in macaques (Agustín-Pavón et al.

2012, Shiba et al. 2015). Indeed, such increased reactivity has now been confirmed in macaques following excitotoxic lesions of not only areas 11 and 13 but also area 14 (Pujara et al. 2019). In the marmoset studies, lesions of either the anterior OFC (antOFC) or vlPFC heightened the pattern of anxiety-like and fear-like responses displayed (**Figure 3*a***). Thus, in response to an innately

a Excitotoxic lesions of antOFC and vlPFC heighten threat responses



b Converging pathways from antOFC and vlPFC onto the insula-amygdala in the regulation of threat



c vlPFC-induced failure to disengage attention and antOFC-induced impairment to reevaluate stimuli

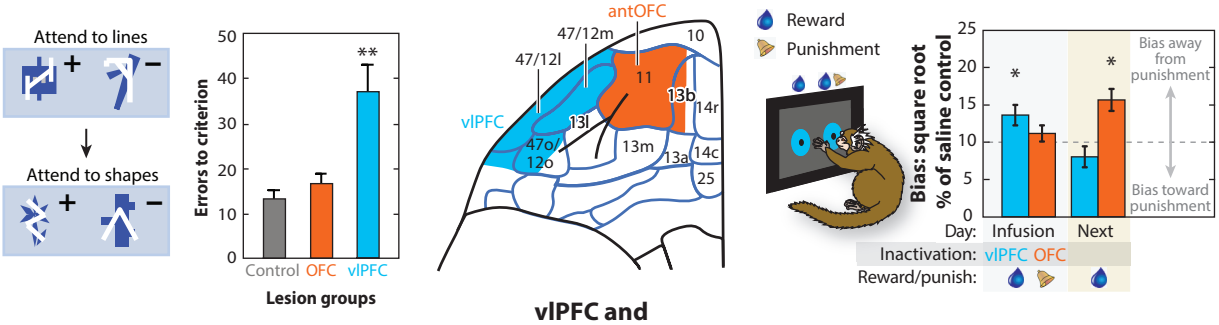


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Figure 3 (*Figure appears on preceding page*)

Distinct prefrontal regions providing independent contributions to threat regulation converge on the insula-amygdala in the marmoset. (*a*) Heightened reactivity to both innate threat (rubber snake) and uncertain threat (unknown human) following excitotoxic lesions of the antOFC and vlPFC in marmosets. Individual grey dots represent non-experimental animals from the colony illustrating the marked individual differences in reactivity to threat in the normal population. While lesions of either antOFC or vlPFC increased threat reactivity, the responses remained within the natural variation of the colony. Data derived from Agustín-Pavón et al. (2012) and Shiba et al. (2015). (*b*) Heightened activity to threat compared to safety in the insula-amygdala in the unlesioned hemisphere is not seen in the insula-amygdala in the lesioned hemisphere. Following a unilateral excitotoxic lesion of either the antOFC or vlPFC, the insula-amygdala on the ipsilateral side shows heightened FDG uptake in both threat and safety conditions. Colored bar in PET images represents FDG-uptake difference between fear and safety conditions (% change) with black being 0%, red 25%, and white 50%. Data redrawn from Shiba et al. (2017). (*c*) Differential effects of antOFC and vlPFC lesions on attentional set-shifting [data redrawn from Dias et al. (1996)] and approach-avoidance decision making [data redrawn from Clarke et al. (2015)]. Marmosets with vlPFC but not antOFC inactivations are much slower to disengage from a previously relevant stimulus dimension, such as lines, and to shift their attention to a previously irrelevant stimulus dimension, such as shapes, in order to learn which exemplar is rewarded. They are also more likely to avoid punishment to a greater degree than controls when confronted with punishment on the approach-avoidance task. In contrast, inactivation of the antOFC does not alter sensitivity to punishment on the day of punishment but influences the memory for punishment, increasing the animals' avoidance of the punished side on the next day. $^{*}p < 0.05$; $^{**}p < 0.01$. Abbreviations: antOFC, anterior orbitofrontal cortex; FDG, fluorodeoxyglucose; OFC, orbitofrontal cortex; PET, positron emission topography; SUVrc, standardized uptake value ratio coefficient; vlPFC, ventrolateral prefrontal cortex.

aversive stimulus (a rubber snake placed in the home cage), marmosets with either OFC or vlPFC lesions, compared to sham-operated controls, spent more time at the back of the cage and showed a reduced number and duration of episodes staring at the snake. Similarly, both groups of lesioned animals also displayed increased avoidance of an unknown human, by spending more time at the back of the cage, and exhibiting reduced locomotion and increased vigilant responding. The only differences to emerge between the two lesioned groups was with respect to vocalizations. While these were markedly reduced in response to the snake in both lesioned groups, in response to the ambiguous human intruder, vlPFC-lesioned animals made more aggressive vocalizations, indicative of the adoption of a more proactive strategy in the face of threat.

The marked increase in reactivity to anxiety-provoking contexts following antOFC lesions in marmosets differs from the apparent lack of effects of lesions to/inactivation of various regions of rodent OFC on the classic tests of uncertainty, including the EPM and open field. Any comparison with primate vlPFC is challenging due to the lack of known homology. Better alignment, though, is seen between studies of OFC in rodents and marmosets investigating responsivity in Pavlovian conditioned threat tests. In marmosets, lesions of neither antOFC nor vlPFC altered the expression of the discriminative conditioned cardiovascular and behavioral threat responses that had developed before the lesion. However, following the experience of a single session in which two out of the four threat-associated CSs were not followed by the expected loud noise (partial extinction), the threat-induced responses of lesioned marmosets appeared more rigid and less flexible than those of controls (Agustín-Pavón et al. 2012). Thus, in the case of OFC disruption, the resulting increase in threat responses is consistent across species (as summarized in **Figure 2**).

Combining lesions of the antOFC or vlPFC with 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG), PET has revealed dysregulation of a common downstream pathway encompassing the anterior insula and dorsal amygdala (**Figure 3*b***). Both lesions abolished the differential uptake of FDG in this pathway during exposure to threat compared to safety, with FDG uptake being as high during safety as during threat (Shiba et al. 2017). This is consistent with neuroimaging studies in humans that have reported negative correlations between prefrontal and amygdala activity in disorders of emotion regulation (Etkin & Wager 2007). Importantly, however, the study in monkeys not only provides evidence for causality but also highlights the contribution of at least two functionally distinct prefrontal regions to the regulation of the amygdala and anterior

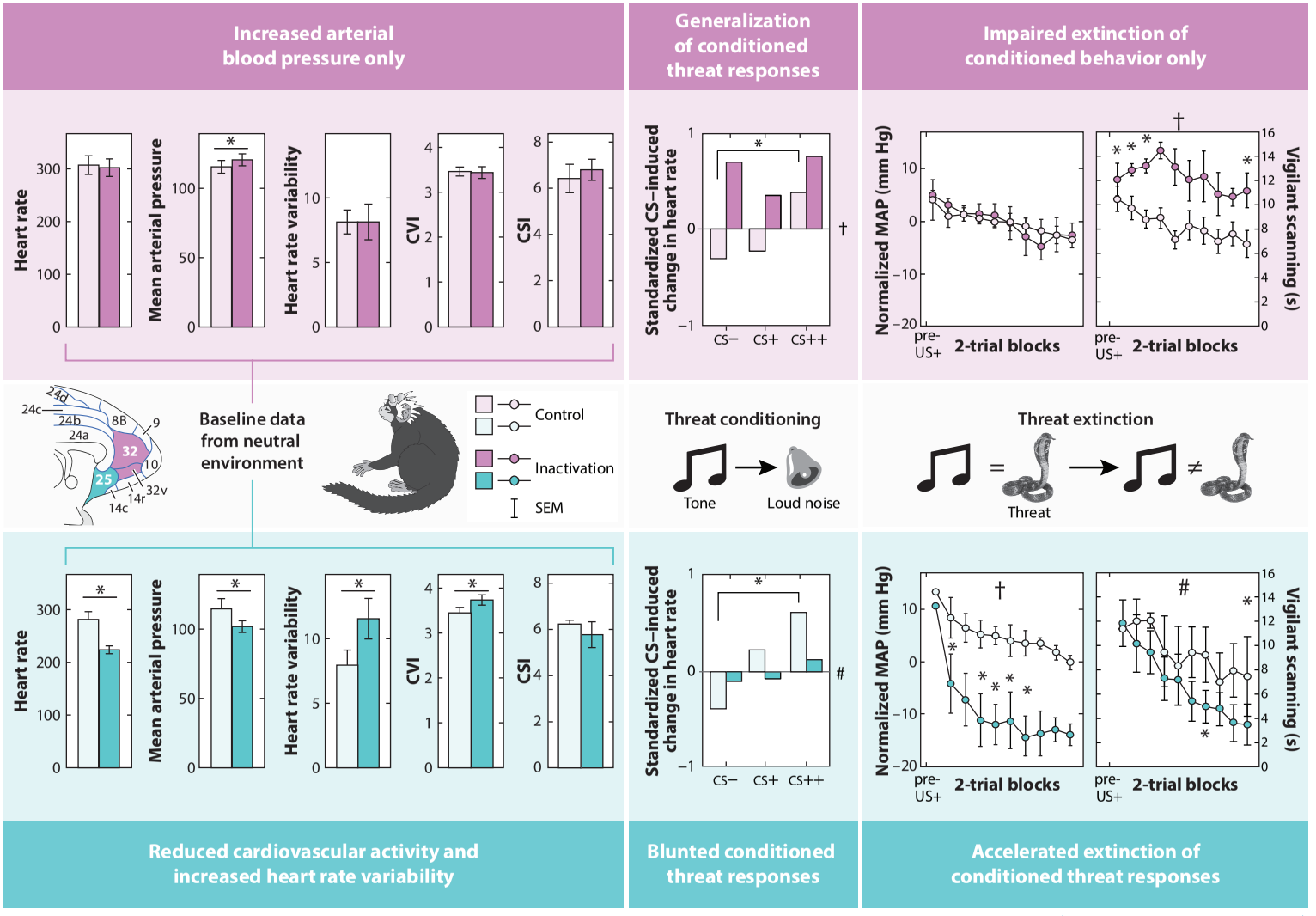
insula. The differential role of these two regions in the regulation of threat-related processing has been demonstrated using an approach-avoidance decision-making task to assess the reactivity of the subject to punishment when in conflict with reward (Clarke et al. 2015). Only inactivation of the vlPFC increased avoidance of the punished side on the day of punishment, while inactivation of the OFC induced an avoidance response the following day in the absence of punishment, apparently based on enhanced memory of the punishment experienced the day before (**Figure 3*c***). The expression of this enhanced punishment memory effect was shown to be dependent upon the amygdala and anterior hippocampus, as the inactivation of either or their disconnection (by unilateral inactivation of each in opposite hemispheres) blocked the antOFC inactivation-induced avoidance response the next day.

In summary, both primate antOFC and vlPFC are involved in the regulation of both conditioned threat responses and anxiety-like responses in contexts of uncertainty, and both act upon a common insula-amygdala pathway in the regulation of these responses. However, the differential effects of antOFC and vlPFC inactivations on punishment avoidance highlight their differential role in this regulation, despite the similar observable anxiety-like phenotype. This is highly relevant to our overall understanding of individual variation in patients suffering from GAD, whereby, for example, two patients presenting in the clinic may appear generally anxious but their anxiety may be produced by distinct underlying psychological dysregulations that may require alternative forms of therapy. This will be discussed in more detail below.

Medial Prefrontal and Anterior Cingulate Cortices

There have been only a handful of intervention studies in primates investigating the functions of medial and anterior cingulate cortices across reward or punishment domains. One study recorded neuronal activity from the perigenual region of macaques, around the border between areas 32 and 24, and revealed a population of neurons coding positive and negative subjective value. Microstimulation of the localized group of negative-encoding neurons enhanced punishment avoidance on an approach-avoidance task, an effect that was subsequently blocked by an anxiolytic (Amemori & Graybiel 2012). Another study showed that low-frequency stimulation that inactivated activity within postgenual dACC (area 24) in macaques disrupted the recall of conditioned threat responses after extinction (Klavir et al. 2012). More recent research has compared the involvement of area 25 and area 32 in the regulation of threat-elicited physiological and behavioral responses in marmoset monkeys using a range of Pavlovian and instrumental paradigms (**Figure 4**). Inactivation of area 25 abolished the CS-induced increase in heart rate and vigilant scanning in anticipation of aversive loud noise in a Pavlovian discriminative conditioning paradigm, and it also promoted more rapid extinction of conditioned threat in an extinction recall paradigm (Wallis et al. 2017) designed to match as closely as possible the one used to study the effects of IL and PL manipulations in extinction recall in rodents (Sierra-Mercado et al. 2010). In contrast, area 32 inactivation resulted in generalization on the Pavlovian discrimination paradigm, such that the CS-induced rise in heart rate and vigilant scanning became indiscriminate, occurring to all CSs regardless of their relationship with aversive loud noise. Area 32 inactivation also impaired extinction of the conditioned vigilant scanning response (but not BP response), with vigilant scanning remaining high across much of the extinction session. Thus, overall, the effects of area 25 and area 32 inactivations in monkeys are opposite to the effects induced by inactivation of their putative homologs in rats (summarized in **Figure 2**), which heighten (IL) and reduce (PL) conditioned freezing responses, respectively (Milad et al. 2006).

Further support for the role of area 25 in threat-elicited behaviors, opposite to that seen in rodents, comes from inactivation studies that reveal amelioration of the physiological and



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

Opposing effects of area 25 and area 32 inactivations on cardiovascular and behavioral arousal. Area 25 inactivations (*lower panel*) reduce behavioral and cardiovascular responses in neutral contexts (*left graphs*) and threatening contexts (*right graphs*), the latter including discriminative Pavlovian conditioned responses to a CS+ associated with aversive loud noise and extinction of Pavlovian conditioned threat with a single cue associated with exposure to a rubber snake. Inactivations of area 32 (*upper panel*) have little effect on baseline cardiovascular activity in a neutral context (*left graphs*), but in threatening contexts (*right graphs*) they cause generalization of conditioned behavioral and heart rate responses to unpaired or partially paired stimuli associated with aversive loud noise. They also prolong conditioned behavioral responses to a stimulus paired with a rubber snake in extinction. Heart rate is measured in beats per minute; mean arterial pressure (MAP) is measured in millimeters of mercury. $^{*}p < 0.05$; $^{\dagger}p < 0.05$ for main effect of inactivation; $^{\#}p < 0.05$ for inactivation × CS interaction. Abbreviations: CS−, stimulus not paired with threat; CS+, stimulus paired with threat on 50% of occasions; CS++, stimulus paired with threat on 100% of occasions; CSI, cardiac sympathetic index; CVI, cardiac vagal index; SEM, standard error of the mean; US+, unconditioned stimulus (snake). Data redrawn from Wallis et al. (2017).

behavioral suppression caused by unpredictable presentations of aversive loud noise in high-trait anxious marmosets (Zeredo et al. 2019), alongside reductions in punishment avoidance on an approach-avoidance task (Wallis et al. 2019) in low- to mid-trait anxious marmosets. Moreover, that area 25 plays a necessary and sufficient role in the top-down regulation of visceral responses was revealed by the reduced cardiovascular activity and accompanying increase in heart rate variability and vagal tone induced by area 25 inactivation during baseline or neutral conditions. In contrast to the overall reduction in negative affective responses following inactivation of area 25, activation induced by the glutamate transporter (GLT-1) blocker dihydrokainic acid heightened anxiety-like responses to uncertain threat in the human intruder test (Alexander et al. 2019b).

Conversely, area 32 inactivation had no effect on the responsivity of high-trait anxious animals to unpredictable threat or on the sensitivity to punishment of low- to mid-trait anxious marmosets in the approach-avoidance task, and it had very limited effects at baseline, selectively increasing BP only. Similarly, overactivation also had no effect on responsiveness to an unknown human. Although the lack of effect on approach avoidance contrasts with the microstimulation effects in the perigenual cingulate in macaques (Amemori & Graybiel 2012), these differences may arise from the fact that microstimulation targeted a very localized set of negative-coding neurons within a larger area of mixed positive- and negative-encoding neurons. Thus, the lack of effect following inactivation of a much larger area in the marmoset is somewhat inconclusive.

ISSUES OF FUNCTIONAL HOMOLOGY

The discrepancies between marmoset and rodent area 25/IL and area 32/PL with respect to the regulation of conditioned threat act as an important illustration of the difficulties in identifying homologous regions across species. Based on a variety of structural characteristics, including cyto-, myelo-, and chemoarchitecture, these regions appear structurally homologous (Vogt & Paxinos 2014), but discrepancies in the functional effects of inactivation call into question whether they are also functionally homologous. Minor changes in task parameters can have a marked impact on the psychological processes underlying performance. This is exemplified by the finding that decreased expression of the conditioned freezing response following PL inactivation is absent if rats have been preexposed to the test apparatus for one or two sessions prior to acquisition of Pavlovian conditioning (reviewed in Sharpe & Killcross 2018). It is argued that preexposure to the test apparatus reduces the saliency of the contextual cues, such that the first time the animals experience the foot shock, the most salient stimulus is the novel CS, which, with little competition from other cues (including contextual cues), enters relatively easily into association with the US. Based on the effects of PL manipulations on a range of other cognitive tests involving competition between cues, Sharpe & Killcross (2018) propose that rodent PL is involved in the learning and

expression of conditioned threat responses through its involvement in attention selection and control. Thus, lesioning/inactivation disrupts cued conditioning only when there is competition between cues. Whether differences between the protocols used to measure conditioned threat in marmosets and in rodents can account for the opposing effects of area 25/IL and area 32/PL remains to be determined.

Although it is too early to rule out functional homology between area 32/PL and area 25/IL in monkeys and rodents, the discrepant results between marmosets and rodents do suggest, at the very least, that the roles of these areas in regulating threat responses are more complex and context dependent than originally thought (for a review on area 25, see Alexander et al. 2019a). At first sight, this discrepancy between rodents and marmosets stands in contrast to the apparent comparability of rodent and human neuroimaging studies with respect to the role of these regions in conditioned threat and extinction recall, as highlighted by Milad & Quirk (2012). However, closer inspection shows that, in comparison to rodent IL, human neuroimaging studies reveal activity within more rostral regions of the vmPFC related to the extinction recall of conditioned autonomic responses (Phelps et al. 2004, Milad et al. 2007b, Dunsmoor et al. 2019) compared to the more caudally located area 25 (as discussed in Myers-Schulz & Koenigs 2012). Thus, it is not so surprising that area 25 inactivation in marmosets fails to disrupt extinction or extinction recall. Indeed, the finding that marmoset area 25 appears to support rather than dampen negative processing is consistent with the general consensus that activity in area 25 in humans is associated with negative affective states (reviewed in Myers-Schulz & Koenigs 2012 and Alexander et al. 2019a). It is worth noting, though, that altered activity in a more caudal subgenual region in humans was associated with the late stages of extinction training in the study by Milad et al. (2007b) but not in the study by Phelps et al. (2004). Marked differences between these two imaging studies—including the use of context (or not) to differentiate conditioning from extinction phases and the presence (or not) of a stimulus unpaired with the US (CS−) or an additional stimulus that is paired with the US (CS+) but that did not undergo extinction—make further comparisons difficult (for additional discussion, see Fullana et al. 2018).

Correspondence between rodent PL and its homologous region in humans is also unclear. Rodent PL has been likened to human dACC, rather than perigenual area 32, based on human neuroimaging studies that have implicated dACC in the acquisition and expression of conditioned threat responses (Milad et al. 2007a). Indeed, dACC in macaques has also been implicated in the acquisition and expression of conditioned threat responses and adaptive aversive learning (Klavir et al. 2012, 2013). However, evidence presented above suggests that rodent ACC (Cg1/Cg2/area 24) is also implicated in conditioned threat responses, although more specifically in the acquisition rather than expression, which could also be related to the dACC findings in human (Milad et al. 2007a) and macaque (Klavir et al. 2012). This is especially relevant since correlations between skin conductance and the activity and thickness of human dACC were reported during the acquisition, rather than expression, phase of conditioning. Moreover, since caudal PL in rodents is now included in area 24 (Paxinos & Watson 2013), future studies should determine whether the disruption of conditioned threat expression in rodents is dependent upon inactivation of rostral PL (recently renamed area 32) or caudal PL (area 24).

EXECUTIVE FUNCTIONS AND EMOTION REGULATION

One major reason the effects of prefrontal and cingulate manipulations on responses to threat can appear more variable between and within rodents and humans/NHPs is the nature of prefrontal regulation itself. As already described for PL, and also true for most prefrontal and cingulate

regions, their involvement in higher-order cognitive mechanisms means that their regulation of behavior is seldom exclusive to emotion-related contexts, and the relationship between cognition and emotion is a complex one. Cognition is an integral part of the appraisal process for a given emotion, and emotions can have a profound influence on cognition (comprehensively reviewed in Joormann & Stanton 2016). There has already been considerable progress in humans in characterizing the different automatic and goal-directed strategies that regulate emotional responding (Ochsner & Gross 2005, Hartley & Phelps 2010, Okon-Singer et al. 2015, Braunstein et al. 2017), and executive functions such as working memory, attentional set-shifting, and response inhibition have all been hypothesized to contribute to this regulation (Ochsner et al. 2012, Joormann & Stanton 2016). These functions are critically dependent upon the vlPFC and dlPFC, and disruption of some of these mechanisms in animals is likely to be responsible for dysregulation of threat-elicited responses. The vlPFC has been implicated in attentional processes in human functional neuroimaging studies (Corbetta & Shulman 2002) as well as primate functional studies (Kennerley & Wallis 2009). In particular, vlPFC lesions in marmosets disrupt the ability to shift attentional set from one perceptual dimension (e.g., shapes) to another (e.g., lines) when performing a series of visual discriminations for reward (Dias et al. 1996). Consequently, the enhanced sensitivity to punishment on the approach-avoidance task following vlPFC inactivation and the increased anxiety in response to a human intruder following vlPFC lesions could be explained by attentional inflexibility or a failure of attentional disengagement. Salient threatening stimuli in the environment naturally capture attention, but in the absence of a flexible attentional system, attention can become focused on the threatening stimulus at the expense of the rest of the environment. The more attention is focused on the negative stimulus, the more anxious a subject is likely to become, thereby enhancing responsivity to a human intruder (Agustín-Pavón et al. 2012) and rubber snake (Shiba et al. 2015) and increasing punishment avoidance in the decision-making task by failing to attend to the continued presence of reward (Clarke et al. 2015).

Such effects are consistent with the difficulties in disengaging attention shown by subjects with MDD in the absence of an initial attentional bias toward negative stimuli (Caseras et al. 2007); importantly, such difficulties have been shown to correlate with mood changes in MDD in response to a stressor (Sanchez et al. 2013) and have been related to altered activity in the vlPFC (see Joormann & Stanton 2016 for a comprehensive review). Moreover, the symptom of rumination has been hypothesized to reflect impaired attentional disengagement (Koster et al. 2011). Attentional flexibility may also be a key requirement in effective reappraisal, although in this case the attentional shifting that correlates positively with reappraisal may be specifically between aspects of affective, rather than nonaffective, material (Malooly et al. 2013).

This attentional account is not unlike the one proposed by Sharpe & Killcross (2018) with respect to PL in rodents. Indeed, they highlight that PL lesions in rats induce similar set-shifting deficits to those reported in marmosets with lateral prefrontal lesions (Dias et al. 1996). It is this apparent similarity that has led to suggestions that rodent PL may share functional homology to primate lateral PFC. Without direct comparison of area 32 manipulations on attentional set-shifting in primates it is difficult to reconcile these findings between primates and rodents. However, they may be consistent with the proposal that there is an expansion and specialization of cognitive functions across the PFC in primates, the rudiments of which are instantiated in rodents in more general control modules, such as those found in the PL.

Similar to lesions of the primate vlPFC, lesions of the primate antOFC also enhance anxiety-like behavior in response to a human intruder, but unlike those of the vlPFC, lesions of this region do not disrupt attentional set-shifting. From studies of reward processing, this region has been implicated instead in reevaluation of the desirability of choices based upon current biological states

and needs (Murray & Rudebeck 2018). Such a hypothesis could account for the enhanced punishment memory of aversive loud noise seen on the approach-avoidance decision-making task in marmosets following antOFC inactivation (Clarke et al. 2015). In the presence of reward, the punishment is reevaluated in order to decide whether to continue approaching to obtain maximum reward or to avoid and thereby accept a lower level of reward. If the antOFC is not "online" at the time of that reevaluation process, the antOFC is unable to predict the updated value when it is back "online" the next day. Reevaluation could also play an important role in tests of uncertainty, including the human intruder test used in monkeys, where the past experience of a laboratory animal with an unknown human is highly variable and thus the value attached to the unknown human is constantly updated. Since the OFC in rodents has also been implicated in this reevaluation process (Sharpe & Schoenbaum 2016, Panayi & Killcross 2018), it would be predicted that OFC lesions/inactivation should also induce enhanced avoidance in open-field and EPM tests. However, one partial explanation for the fact that OFC lesions in rodents do not show consistent effects on these tests may be the high variability between studies of the extent of the lesion across functionally distinct regions of the OFC (discussed in Panayi & Killcross 2018), along with the relative paucity of the measurements used to determine the emotional reactivity of the animal in these tests.

CONCLUDING REMARKS

Experimental studies of the prefrontal regulation of threat processing, compared to reward processing, have suffered from a relative paucity of tests used to study threat responsivity in animals and humans. In part this is due to the nature of threats and also the difficulty of applying them in a laboratory setting. There is asymmetry in the response to predictions of threat and reward. Predictions of reward increase the chances of experiencing reward again, while predictions of punishment decrease the likelihood of experiencing punishment again. Also, while reward prediction increases approach and engagement with a stimulus, punishment prediction can result in freezing, flight, fight, or, in the case of uncertainty, partial engagement (discussed in Boureau & Dayan 2011). By exploiting a wide range of rewards, such as different foods and liquids, studies of reward processing have dissected out the discrete role of specific regions of the ventral PFC in predicting rewarding outcomes based on their ability to update the value/desirability of an outcome, determine its likelihood, and compare values across dissimilar commodities (Murray & Rudebeck 2018). Reevaluation, likelihood, and comparison of negative outcomes may depend upon the same broad regions within the ventral PFC, albeit embedded in distinct output circuits given the differences in the nature of the responses. Future studies should develop tests that exploit these distinctions in the negative domain in order to gain more insight into the underlying regulation of threat processing.

Paradigms such as the human intruder test in monkeys have proven useful in detecting heightened threat responsivity following localized antOFC and vlPFC excitotoxic lesions and following overactivation of area 25, but they cannot so easily dissect out the distinct underlying causes. Instead, tests such as the approach-avoidance paradigm have begun to provide insight, helping to elucidate the specific cognitive processes within distinct prefrontal regions of the NHP that, if dysregulated, may induce more rigid threat and anxiety-like responses. In rodents, open-field tests and the EPM need to be replaced by more discerning tests of threat uncertainty that can be varied in terms of threat evaluation and likelihood. These can include Pavlovian conditioning paradigms in which threat is uncertain (Davis et al. 2010) but also more ethological-based tests that can include distance from the threat as a variable, allowing for the expression of a range of behaviors (Mobbs & Kim 2015). In addition, since autonomic responses are a major component

of the response to threatening stimuli, they should be taken more into account in the animal literature, especially because they are the measures most commonly used in studies of emotional states in humans and show profound alterations in anxiety disorders. The use of more sophisticated but comparable tests and measurements across humans and animals will aid in translation, especially if the psychological concepts underlying these tests are exported into the clinic. For example, attentional biases toward negative stimuli (Carlisi & Robinson 2018) and enhanced sensitivity to negative feedback (Murphy et al. 2003), commonly associated with mood and anxiety disorders, can be effectively studied across species using similar paradigms (Bari et al. 2010, Rygula et al. 2015, Aylward et al. 2019). However, all this will only be successful if we more readily acknowledge any differences in results between species and recognize that the establishment of functional homology cannot be based upon the results of one test.

Renewed focus on the executive functions of the PFC, including working memory, planning, and attentional set-shifting, will contribute enormously to our understanding of the prefrontal regulation of threat processing. For example, there have been no intervention studies of the dlPFC (areas 46 and 9) on threat processing in monkeys, although altered dynamics within the executive network that includes dlPFC and between that network and others is reported in anxiety disorders (Suo et al. 2017, Coplan et al. 2018). Indeed, reduced functional connectivity between the dlPFC and the central nucleus of the amygdala has been described in young rhesus monkeys and children with a high anxious temperament (Birn et al. 2014). Areas 46 and 9 have no direct connections with the central nucleus but do have weak connections with the neighboring basal nucleus. Moreover, neuroimaging has highlighted indirect connectivity of the dlPFC with subcortical threat circuits via the vmPFC (reviewed in Hartley & Phelps 2010). Thus, future studies should also determine the interactions of these distinct regions of the PFC in monkeys in order to establish their causal role in emotion regulation.

FUTURE DIRECTIONS

1. Future research should dissect out the precise psychological mechanisms that underlie the involvement of distinct regions of the prefrontal and anterior cingulate cortices in the processing of threat in animals and should relate them, where possible, to strategies of cognitive regulation of emotion in humans.
2. It is necessary to develop new tests for the study of threat processing across species, including humans, that allow the different aspects of threat predictability, threat evaluation, and reevaluation to be studied independently. It is also important to have multiple physiological and behavioral measures.
3. The results from (1) and (2) above should act as catalysts for a better understanding of cross-species homologies in prefrontal and anterior cingulate function and thus facilitate translation.
4. Futures studies should determine the nature of the hierarchical interactions within the prefrontal and anterior cingulate cortices in the regulation of threat processing, e.g., lateral prefrontal cortex and area 25 in human and nonhuman primates, and areas 32 and 25 in rodents.
5. Researchers should identify the neural circuits upon which existing therapies act to provide effective treatment as well as to identify new circuits and thus alternative therapies.

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The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as effecting the objectivity of this review.

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